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Vaginal primary malignant melanoma of a Chinese woman: an exceptionally rare yet lethal case report and literature review

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Summary

Vaginal primary malignant melanoma is an exceptionally rare, especially in Taiwan, yet lethal disease, with a five-year overall survival rate of only 18%. Recent elucidation of alternating pathogenesis and refinement of diagnostic methodologies are vital for future management standardization. The authors describe a case of a 58-year-old postmenopausal Chinese woman with vaginal malignant melanoma, with vaginal spotting and vulvar itching as initial presentation. After immunohistochemical staining of biopsy specimen had shown positive of S-100 and HMB-45, and total vaginectomy with bilateral inguinal lymphadenectomy was performed. The patient remains free of disease six months after discharge. In conclusion, vaginal primary malignant melanoma with initial presentation mimicking vaginitis and symptomatic menopausal state could cause diagnostic confusion, especially at postmenopausal woman. By understanding clinical presentation, pathogenesis, differential diagnosis, and treatment options of vaginal primary malignant melanoma, effective diagnosis could be possible.

Key words: Vaginal melanoma; Taiwanese; Vaginectomy; S-100; HMB-45; BRAF mutation.

Introduction

Vaginal primary malignant melanoma is an exceptionally rare (only 1-2% of all gynaecological malignancies) yet lethal (five-year overall survival rate was only 18%) disease that accounts for only 2.4−2.8% of all vaginal malignancies. Frequencies of BRAF mutation in vaginal melanoma ranging from 0−12.5%, and mutation of NRAS and c-KIT were 12% and 0%, respectively. Vaginal bleeding was the commonest presentation for vaginal melanomas, ranging from 60−100%. Poor survival was significantly associated with increasing Breslow depth, presence of lymph node metastases, and those unamenable to surgical resection. Conservative wide local excision of primary tumor remains the preferred primary management.

Case Report

A 58-year-old postmenopausal Chinese woman, gravida 2, para 2, was admitted to Taipei Municipal Wanfang Hospital because of daily vaginal spotting for 45 days. The patient had been in her usual health until 45 days before this admission, when persistent vaginal spotting and intermittent vulvar itching developed. The vaginal spotting was reportedly bright red in colour without associated unusual or foul smelling. The patient had to change overnight pad twice a day for this reason. The patient presented at gynaecology outpatient clinic of this hospital 21 days before admission for consultation. On gynaecological examination, there had been reportedly a 2.5-cm irregular shaped mass lesion with contact bleeding on right lateral vaginal wall; the other physical examinations were otherwise normal. The vaginal cuff was smooth and no palpable mass was revealed at cul-de-sac and parametrium. No palpable inguinal lymph node was reported. Ultrasound showed no significant abnormal findings. Two mucosal irregular protruding mass lesions were found in the lower third of vaginal wall under colposcopy (Figure 1).

On presentation one day later, vaginal incisional biopsy of specimens obtained from pigmented lesions were sent for histopathological examination. Microscopic sections demonstrate malignant melanoma. Immunohistochemical staining revealed positive for S-100 and HMB-45 (Figures 2A and 2B), and Ki-67 proliferative index was 70%.

Five days before admission, MRI of abdomen and pelvis with and without Gd-DTPA enhancement revealed vaginal melanoma without paravaginal tissue invasion and regional and para-aortic lymph node enlargement. The patient was admitted to this hospital.

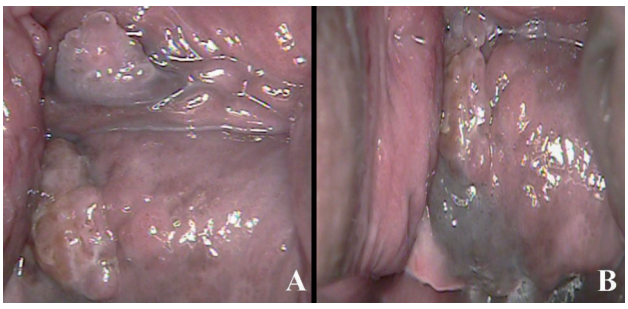

Figure 1. — Colposcopic findings. Two mucosal irregular protruding mass lesions with ill-defined fuzzy gray-coloured border originate at the eight o'clock position (with 2.5 cm in largest basal diameter) and at 11 o'clock (1 cm in largest basal diameter) in the lower third of vaginal wall, with focal erosion.

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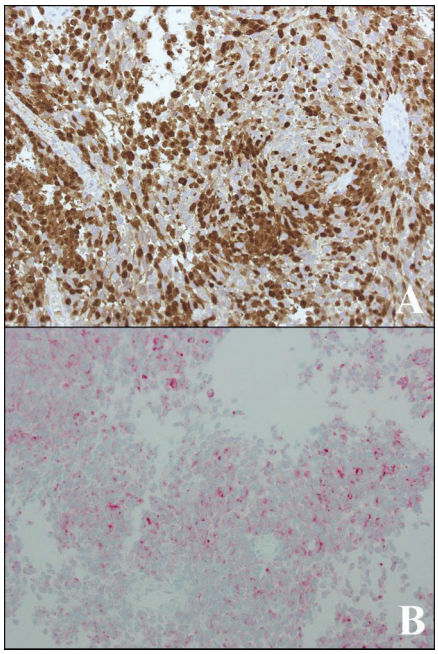

Figure 2. — Incisional biopsy specimen of vaginal pigmented lesions. Immunohistochemical staining demonstrates positivity for S-100 and HMB-45.

At 38 years of age, the patient had had abdominal total hysterectomy in another healthcare centre due to uterine myoma, and no hormone replacement therapy was prescribed ever since. The patient was born in Taiwan and had no contact or overseas travel history. She was married and did not have trauma or unsafe sex history, did not smoke, drink alcohol or use illicit drugs, and had a family history of hypertension.

The next day, a total vaginectomy with bilateral inguinal lymphadenectomy was performed; the result of surgical pathologic analysis was revealed on the third day (Figure 3). Microscopically, sections showed a picture of nodular type malignant melanoma involving the vaginal wall. The circumferential margins were 4.5 mm from the tumour. The vulva included was not involved by the tumour. All inguinal lymph nodes displayed no metastasis of malignant melanoma. The patient had no complications associated with the procedures and was discharged eight days later. During the next six months, at outpatient visits, the patient reported no significant discomfort and no recurrence was revealed.

Discussion

Female genital melanomas are rare primary gynaecological malignancy involving mainly vulva (76.7%) and vagina (19.8%), followed by cervical melanoma, uterine, and ovarian melanomas [1-3]. Primary vaginal malignant melanoma is an exceptionally rare [4, 5], yet lethal disease that accounts for only 2.4–2.8% of all vaginal malignancies [4, 6] and only 1-2% of all gynaecological malignancies [6]. Vaginal melanoma has no known predisposing risk factors and its race distribution is lacking [5]. Majority of the patients were diagnosed in their sixth decade of life, with median age of 62 years [4, 7, 8].

Primary malignant melanomas arise from melanocytes. In general, most melanoma is of cutaneous origin. However, extracutaneous melanomas can also arise in various forms according to distributions of melanocytes, namely ocular melanomas, mucosal melanomas, and leptomeningeal melanomas. Melanomas in internal organ have also been reported in rare cases. Primary mucosal melanomas arise in mucosal epithelium with distribution of melanocytes (Table 1) [9].

Etiology of vulvar and vaginal melanoma are largely unknown. Recent cumulative analysis combining various studies on oncogenic mutations in primary gynaecologic

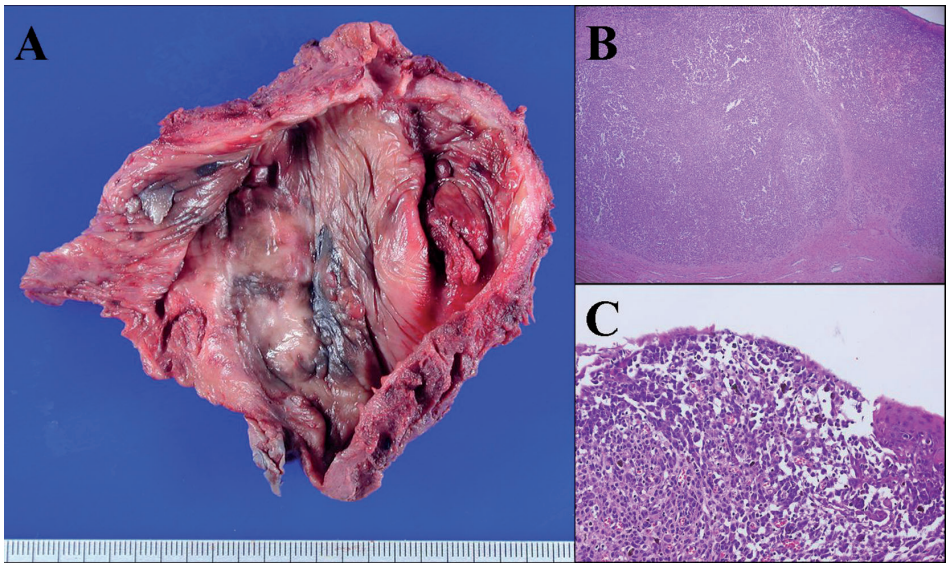

Figure 3. — Surgical pathologic analysis. Gross, (A) an ill-defined irregular black patch on the mucosa, measuring up to 4.8×4.2 cm in dimensions involving posterior and right lateral vaginal wall, is located 1.5 cm above vaginal orifice. Microscopically, (B) nodular type malignant melanoma involving the vaginal wall is revealed. The tumour invades the vaginal wall with invasive depth up to three mm. (C) Focal melanin deposition is presented and focal erosion is revealed at the surface of the tumour.

Table 1. — *Mucosal epithelium with distribution of melanocytes:*

Oral cavity
Esophagus
Ano-rectal canal
Nasal cavity
Paranasal sinuses
Larynx
Vulva and vagina
Cervix

Table 2. — *Differential diagnosis of vaginal melanomas:*

Vaginal melanoma
Adenocarcinomas
Small cell carcinomas
Sarcomas
Lymphoma
Leiomyosarcoma
Schwannoma

Table 3. — *Recommended tumour depth equivalence clinically negative margin:*

Tumour depth	Recommended clinically negative margin
In situ disease	0.5 cm
Breslow thickness less than or equal to two mm	1.0 cm
Breslow thickness greater than two mm	2.0 cm

melanomas has shown that BRAF mutations on gynaecologic mucosal melanomas are 5%, with frequencies of BRAF mutation in vaginal melanoma ranging from 0-12.5% [10]. Mutation of NRAS and c-KIT in vaginal melanoma were 12% and 0%, respectively [11]. In contrast, up to 62% of the malignant cutaneous melanomas arising from sun-exposed skin are driven by oncogenic BRAF mutations [11]. NRAS and c-KIT mutations have been reported in 24% and 17% of chronic sun-damaged cutaneous melanomas, respectively [5, 11]. The results of vaginal melanomas were indeed of startling distinction to those discovered on cutaneous melanomas, suggesting the presence of alternative pathogenetic mechanisms operating in gynaecological melanomas.

Vaginal bleeding was the commonest presentation for vaginal melanomas, ranging from 60−100% [5]. Other symptoms, such as vaginal mass lesions, pain, or discharges were also reported [4, 5, 8]. Worth mentioning is the fact that 11% of patient were asymptomatic at presentation and discovered incidentally [5]. Unlike the aforementioned case in which two tumour masses were located at the lateral and posterior vaginal wall, the tumour was most frequently located in the distal third of the anterior vaginal wall. At presentation, 45% of vaginal melanomas were located at the anterior vaginal wall; 32% and 24% of them were located at posterior vaginal wall and lateral wall, respectively [4, 8]. Sixty-five percent of the patients demonstrated distal third vaginal mass lesions. Majority of these lesions were hyperpigmented melanocytic with minority of them being amelanotic [5]. Pelvic or inguinal nodal involvement was reportedly between 25% and 50% [5, 8], and the commonest sites of distant recurrence were lungs and liver [5].

Malignant vaginal melanomas are particularly aggressive tumours associated with poor overall survival when comparing with cutaneous melanoma. The overall five-year-survival rate of women with genital melanoma is 50.7% [7]. Unfortunately, the five-year overall survival rate was only 18% for female with vaginal melanoma. Five-year-progression-free and median progression-free survival are 9.5% and 11.4 months, respectively [5]. On the other hand, in western populations with high incidence rates of cutaneous melanoma, survival of cutaneous melanoma has significantly improved in recent decades due to the success of early detection and primary preventive campaigns [12]. The overall five-year-survival of cutaneous melanoma for female is 81% [13]. The outcome of vulvar melanoma and vaginal melanoma are the worst among melanomas [7, 14], and this poor patient survival is significantly associated with increasing Breslow depth, presence of lymph node metastases, and those unamenable to surgical resection [7, 11] - the most important prognostic factor is the stage at presentation [6].

MRI is vital in accurate preoperative staging, planning effective management, and monitoring tumour response to therapy. Other than the aforementioned, MRI was suggested to be used to differentiate vaginal melanoma from other vaginal epithelial tumours and non-epithelial tumours. Hyperintense signal on diffusion-weighted imaging (DWI) with a mean apparent diffusion coefficient (ADC) 0.647×10^{-3} mm^2/s has been demonstrated on vaginal melanoma [15].

Immunomarkers are crucial to melanocytic differentiation, as diagnosis and identification of vaginal melanoma can be difficult due to interference caused by the presence of ulceration, the absence of pigment in amelanotic melanoma, and in some of the invasive parts, and the confusing histologic features (Table 2). S-100 is the most sensitive marker for melanocytic differentiation, meanwhile, HMB-45 is more specific for melanocytic differentiation. When S-100 is negative or only focally positive, Tyrosinase and Melan-A (MART-1) are also useful markers [6].

Conservative wide local excision of primary tumour with clinically negative margin (Table 3) remains the preferred primary management of resectable vaginal melanoma. Although surgery significantly increased the survival than those treated nonsurgically [5], aggressive surgeries have shown no significant prognostic alternation in patients with vaginal melanomas compared with wide local excisions with one- to two-cm clinically negative margins [4, 5]. A recent study suggested that radical surgical approach, including hysterectomy, for early-stage vaginal melanoma, should be avoided because early-stage patients who underwent conservative surgery are likely to survive longer [4]. Completion lymphadenectomy is not necessary if sentinel lymph node (SLN) mapping during staging of a newly di-

agnosed patient is negative [5].

Therapeutic agents for advanced and recurrent unresectable melanomas are limited despite the high recurrence rate; approximately 20% of vulvar melanoma and 80% of vaginal melanoma will recur. High-dose interleukin-2 (IL-2), dacarbazine, ipilimumab, vemurafenib, trametinib, pembrolizumab, and nivolumab are the currently U.S. Food and Drug Administration (FDA) approved agents. Due to low BRAF mutation frequencies in vaginal melanoma (0−12.5%), the use of vemurafenib that target specifically against BRAF mutation may not significantly lead to increased survival rates as on chronic sun-damaged cutaneous melanomas [11]. Although specific trials for vaginal melanomas are lacking and effectiveness of these agents on vaginal melanomas remain uncertain [14], a recent study indicated that novel treatment approaches in melanomas of vulva and vagina could be beneficial by targeting of NRAS-mutated tumours with MEK inhibitiors [11].

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