Primary malignant melanoma of the vagina: Case report and review of literature

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Summary

Primary vaginal malignant melanoma is rare, with < 250 reported cases to date. It accounts for < 1% of all melanomas in women, < 10% of all female genital tract melanomas, and < 3% of all vaginal malignancies. Its clinical behavior is notoriously more aggressive than that of cutaneous and vulvar melanoma, with a 5-year survival rate ranging from 5% to 25%. Tumor size is the strongest predictor of survival, whereas tumor thickness is a weak predictor of survival. A case of F.I.G.O. stage I vaginal melanoma encircling and embracing the entire circumference of the middle third of the vagina is described. Tumor size and thickness were 6 cm and 9 mm, respectively. The patient was treated by wide local excision and pelvic radiotherapy, and to date, 11 months after surgery, she is alive and with no evidence of disease. It is concluded that wide local excision followed by pelvic radiotherapy is an appropriate treatment for melanoma confined to the vagina.

Key words: Vaginal malignancy; Wide local excision; Radiotherapy; Tumor size; Microstaging; Tumor thickness.

Introduction

Primary malignant melanoma of the vagina is an aggressive and rare malignancy, with fewer than 250 reported cases to date. It accounts for only 0.3% - 0.8% of all melanomas in women, with an estimated incidence of 0.026/100,000 women per year [1]. It constitutes < 3% of all vaginal cancers, whereas squamous cell carcinoma accounts for 90% - 95% and clear cell adenocarcinoma accounts for 5% - 10% [2-5]. Although, after the vulva, the vagina is the second most common site of melanomas in the female genital tract, vaginal melanoma accounts for only 2% - 5% of female genital tract melanomas [2, 3, 6]. The outcome of patients with vaginal melanoma has been reported to be poor, with an overall 5-year survival rate ranging from 5% to 25% [1-4, 6-9]. Because of its rarity, most reports include singular cases or series of patients in which patient accrual occurred over a prolonged period of time during which treatment approaches and modalities changed. Consequently, very few individuals and even referral centers can build up an adequate experience related to this disease.

We describe a patient with primary vaginal malignant melanoma and a review of the pertinent literature. This patient is one of two patients with primary vaginal melanoma managed at the Soroka Medical Center (SMC) from its inauguration in January 1961 until to date. The other patient was a 95-year old frail woman who died from heart disease shortly after diagnosis of vaginal melanoma. During this 41-year period, 1,814 malignancies of the female genital tract, including six (0.33%) vaginal malignancies (4 squamous cell carcinomas and 2 melanomas), were diagnosed; thus, two vaginal melanomas accounted for 0.11% of all female genital tract malignancies and 33.3% of all vaginal malignancies. During this period, six melanomas of the female genital tract (4 vulvar and 2 vaginal melanomas) were diagnosed; thus, two vaginal melanomas accounted for 33.3% of all female genital tract melanomas.

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Case Report

A 67-year-old, gravida 1, para 1, married postmenopausal Sephardic Jewish woman was admitted in January 2001 because of vaginal bleeding of one month's duration. Menarche had occurred at age 16. Menses, until menopause at age 48, had been regular with a 28-day cycle and flow lasting five days. She had not received hormone replacement therapy and until one month prior to her admission had not experienced postmenopausal bleeding. Her past medical history included a cesarean section, arterial hypertension and allergy to penicillin. Her family history was unremarkable.

Physical examination disclosed an essentially healthy appearance and normal vital signs. Inspection of the external genitalia revealed an apparently normal vulva. Speculum examination of the vagina revealed a dark ulcerated and bleeding lesion, measuring 6 x 4 cm, encircling and embracing the entire circumference of the middle third of the vagina leaving the upper and lower thirds of the vagina free of lesion. The uterine cervix was apparently normal and Papanicolaou smear showed normal cells. Bimanual pelvic examination disclosed a normal sized uterus, no adnexal masses and no involvement of the rectovaginal septum. Endocervical curettage revealed a benign endometrial polyp. Biopsy of the vaginal lesion demonstrated malignant melanoma. Immunohistochemical staining was positive for MART-1 (Melanoma Antigen Recognized by T cells), S-100 and HMB-45 (markers for melanoma), and negative for CK-903 (marker for squamous epithelium), LMW-K (marker for non-squamous epithelium) and actin (marker for smooth muscle). Meticulous examination of the entire body did not disclose additional lesions and fundus examination of both eyes demonstrated normal findings. Computerized tomography

(C.T.) scanning of the brain, chest, abdomen and pelvis, ultrasound examination of the abdomen and pelvis, magnetic resonance imaging (MRI) of the brain and pelvis, isotopic bone scanning and Gallium scanning, mammography, rectoscopy and cystoscopy did not disclose abnormal findings. Since the tumor was limited to the vaginal wall without spread into the paracolpos, rectovaginal septum, bladder and urethra, and there was no evidence of distant metastases, it was clinically allocated F.I.G.O. Stage I.

A wide local excision of the tumor was performed using two circular incisions, one above and one below the tumor. The vaginal segment (middle third of the vagina) between these two incisions was meticulously undermined and separated from its surroundings and removed. Microscopic examination demonstrated predominantly epithelioid type malignant melanoma (Figure 1) with the presence of vascular and perineural invasion (Figure 2), extensive ulceration and mild to moderate pigmentation. Tumor size was 6 cm in its greatest dimension, and tumor thickness (Breslow) was 9 mm. All surgical margins (deep and lateral) were involved with tumor. The patient made an uneventful postoperative recovery; the vaginal wound healed primarily and although the vagina was shortened by more than a half, it remained patent and no vaginal tumor or pigmentation could be identified.

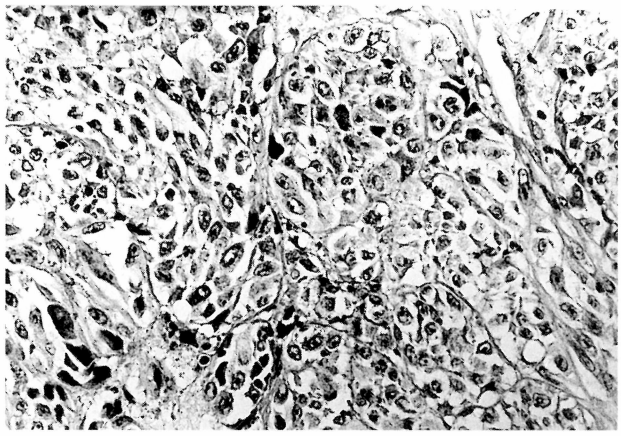

Figure 1. — Primary vaginal malignant melanoma. Tumor composed of epithelioid cells with round and oval nuclei that show prominent nucleoli. Some to the cells are pigmented (H&E x 400).

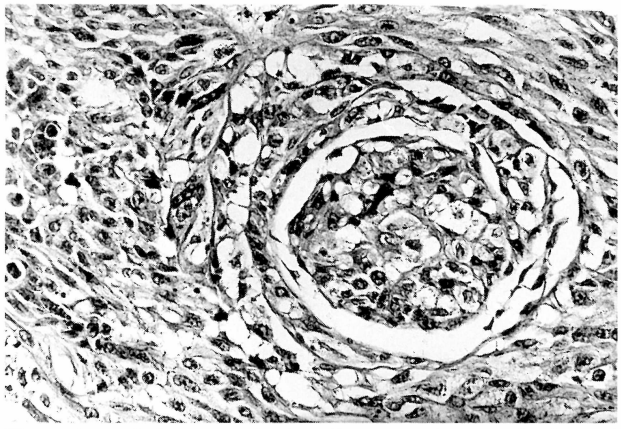

Figure 2. — Primary vaginal malignant melanoma. Perineural invasion (H&E x 400).

Postoperatively, three consecutive vaginal intracavitary applications of high-dose rate brachytherapy (each application: vaginal surface dose of 700 cGy) via a vaginal cylinder (Delclos) was given. This was followed by external megavoltage photonic irradiation employing a 10 MeV linear accelerator delivering 5,040 cGy to the whole pelvis, including the inguinal regions, in 28 daily fractions of 180 cGy via AP-PA opposed fields. She tolerated radiotherapy well and to date, 11 months after initial diagnosis, she is alive and well and without evidence of disease.

Discussion

At the SMC, vaginal cancers accounted for only 0.33% of all female genital tract malignancies. Vaginal melanomas accounted for 33.3% of all vaginal cancers and 33.3% of all female genital tract melanomas. These findings do not corroborate previous studies that demonstrated that vaginal cancers account for 1% - 2% of all female genital tract malignancies, and vaginal melanomas account for < 3% of all vaginal cancers and 2% - 5% of all female genital tract melanomas [2-6]. However, in Weinstock's series, which included 203 vulvar and 51 vaginal melanomas collated from several population-based cancer registries in the United States, vaginal melanoma accounted for as much as 20% of all female genital tract melanomas and the incidences of vulvar and vaginal melanoma was estimated to be 0.108/100,000 and 0.026/100,000 women per year, respectively [1].

Primary vaginal malignant melanoma is defined as melanoma originating in the vaginal wall without involvement of the vulva and/or the uterine cervix. Melanoma of the vagina appears to originate from melanocytes that are present in the vaginal mucosa of approximately 3% of women [2, 3]. These lesions are usually pigmented; less than 10% lack pigmentation (amelanotic) [6]. It has been shown that melanomas occur more commonly in the lower third of the vagina and more often on the anterior vaginal wall [2-7]. In this patient, however, the melanoma was encircling and embracing the entire circumference of the middle third of the vagina leaving the upper and lower thirds of the vagina free of lesion.

The age at the time of diagnosis of this patient was 67 years. This is in agreement with studies that showed that patients with vaginal melanoma typically present in the sixth and seventh decades of life [1,3,4,6,7,9]. It has been claimed that vaginal melanoma, like vulvar melanoma, is particularly uncommon among black women [9], but Weinstock [1] in an epidemiologic study of 51 cases of vaginal melanoma could not confirm that. Hence, Weinstock [1] has suggested that black women are relatively protected against vulvar melanoma but not vaginal melanoma.

The most common presenting symptom of vaginal melanoma is bleeding, although it may also present as a mass or with discharge or dyspareunia [1-7]. Irvin et al [3] have shown that the time interval between the onset of symptoms and seeking medical attention ranged from 2 days to 4 months, with a mean of 2.4 months.

The prognosis of patients with vaginal melanoma has been shown to be notoriously dismal with an overall 5-year survival rate ranging from 5% to 25% [1-3, 6-9]. In comparison, the overall 5-year survival rate of patients with vulvar melanoma has been reported to be as much as 50% [1]. Two meta-analysis studies of vaginal melanoma have been performed so far; Reid *et al.* [10] analyzed in 1989 130 cases and Buchanan *et al.* [2] analyzed in 1998 an additional 67 cases. Of the 67 patients with vaginal melanoma analyzed by Buchanan *et al.* [2], only 18 had survived five years or more and only three had survived 10 years or more. Because of the rarity of this disease, it has been difficult to identify independent factors that affect the prognosis of patients with vaginal melanoma. Factors like age, gravidity, parity, presence of symptoms, tumor cell type, tumor location in the vagina, and F.I.G.O. stage have not been found to be significant predictors of survival. In the above-mentioned two meta-analysis studies [2, 10], tumor size (< 3 cm versus ≥ 3 cm) was the strongest and the only significant predictor of survival. Reid *et al.* [10] have shown that patients with tumor size < 3 cm had significantly better outcome than patients with tumor size ≥ 3 cm ($p = 0.024$). Buchanan *et al.* [2] have demonstrated that patients with tumor size < 3 cm had a mean survival of 41 months compared with 12 months for those with tumor size ≥ 3 cm ($p < 0.0024$). In a series of 14 patients, Petru *et al.* [7] have shown that 3/7 patients with tumors ≤ 3 cm survived longer than five years compared to 0/7 patients with tumor > 3 cm.

In contrast to cutaneous and vulvar melanoma, the importance of microstaging in predicting the outcome of patients with vaginal melanoma has as yet not been established. Since structures equivalent to papillary and reticular dermis and subcutaneous fat are virtually absent in the vagina, microstaging by the method of Clark *et al.* [11] designed for cutaneous melanoma is not applicable to vaginal melanoma. Moreover, even the modification proposed by Chung *et al.* [12] for vulvar melanoma, does not seem to be suitable for vaginal melanoma. Only microstaging by the method proposed by Breslow [13] (tumor thickness measured in millimeters from the tumor surface to its deepest penetration) is applicable to vaginal melanoma. Reid *et al.* [10] have noticed that tumor thickness ≤ 6 mm was associated with a longer disease-free interval when compared to tumor thickness > 6 mm, but tumor thickness did not significantly affect the survival of the patients. Buchanan *et al.* [2] have demonstrated that tumor thickness was not a significant predictor of survival at any of the depths analyzed, although there was a tendency toward significance at depths > 8 mm ($p < 0.0778$). Tumor thickness was recorded in 51 patients collated from several reports [6]; in 11 patients with tumor thickness < 2 mm the mean survival time and the 5-year survival rate were 60 months and 36%, respectively, whereas in 40 patients with tumor thickness > 2 mm the mean survival time and 5-year survival rate were 27 months and 12.5%, respectively. Thus, it has been suggested that tumor thickness < 2 mm implies improved survival. Noteworthy, most patients with vaginal melanoma present with advanced tumor thickness, probably due to delayed diagnosis because of the location of the lesion in the vagina and late presenting symptoms [7].

The optimal treatment for vaginal melanoma has been the subject of debate. Some authors [4, 14] have noticed an improved locoregional control and possibly better overall survival with radical surgery (vaginectomy or pelvic exenteration), whereas others [2, 3, 6] have found no significant difference in outcome between conservative surgery (wide local excision), radical surgery, radiation therapy, or chemotherapy. Since no advantage of radical surgery over conservative surgery could be demonstrated, Buchanan *et al.* [2] have found it difficult to support radical surgery as primary treatment for vaginal melanoma unless necessary to achieve clear tumor margins. It has been shown that excellent locoregional control may be obtained with the use of wide local excision followed by external pelvic radiotherapy (teletherapy) plus brachytherapy, without the attendant morbidity and physical disfigurement associated with radical surgery [3, 6, 7]. Petru *et al.* [7], have demonstrated that patients with tumor ≤ 3 cm who received either primary radiotherapy or adjuvant radiotherapy after wide local excision exhibited a better survival compared to patients who did not have radiotherapy. Irvin *et al.* [3] have suggested that a better locoregional control may be obtained when the external radiotherapy is administered in high-dose fractions (> 400 cGy per fraction). Our patient received adjuvant radiotherapy with three applications (each application, 700 cGy) of high-dose rate brachytherapy followed by 28 daily standard-dose fractions (180 cGy per fraction) of external pelvic radiotherapy. Although the surgical margins were involved and tumor thickness was 9 mm, locoregional control has been achieved and maintained until to date. The role of chemotherapy in patients with distant spread of vaginal melanoma has as yet not been established [6, 7]. Immunotherapy methods in vaginal melanoma presented to date have been anecdotal [9].

Conclusion

Vaginal melanoma is rare and associated with a dismal prognosis. It is > 300-fold less common than cutaneous melanoma and has been reported to be 5-fold to 50-fold less common than vulvar melanoma. At the SMC, it was 3-fold less common than vulvar melanoma. Its prognosis is 2-fold to 10-fold worse than that of vulvar melanoma with an overall 5-year survival rate ranging from 5% to 25%. Tumor size has been identified to be the strongest predictor of survival, whereas tumor thickness has emerged to be a weak predictor of survival. Since it has been demonstrated that radical surgery has no significant advantage over conservative surgery, it is difficult to support the use of radical surgery as the primary surgical treatment for vaginal melanoma. Based on literature data and on the case of this patient, it seems that wide local excision followed by radiotherapy is an appropriate treatment for melanoma confined to the vagina.

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