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Case Report

Primary malignant melanoma of the vagina with repeated local recurrences and brain metastasis

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Abstract

Malignant melanoma of the vagina, a very rare malignancy, has a notoriously aggressive behavior associated with a high risk of local recurrence and distant metastasis. At present, there are various treatment options for this disease but no standard guideline. We describe a case of a 54-year-old woman with a locally advanced melanoma of the vagina, who underwent radical surgery, biochemotherapy with interferon-α-2b, chemotherapy, radiotherapy, and repeat excision of local recurrent lesions and brain metastasis. In conclusion, malignant melanoma of the vagina has a high risk for local recurrence. Repeated local excision followed by biochemotherapy is a tolerable treatment.

Keywords: Biochemotherapy; Brain metastasis; Melanoma; Vagina

1. Introduction

Malignant melanoma of the vagina is a very rare malignancy; fewer than 300 patients have been reported to date. The aggressive tumor has a poor prognosis, with 5-year survival rates of 5–25%.[1–3] Different surgical treatment options have been discussed, including radical surgery, exenteration, wide local excision with pelvic lymphadenectomy, and sentinel node biopsy. Various adjuvant therapies have been administered, including radiotherapy (R/T), chemotherapy (C/T), immunotherapy, and biochemotherapy (immunotherapy with C/T). The optimal treatment for vaginal melanoma has been a subject of debate. We describe a case of malignant melanoma of the vagina and review current treatments.

2. Case report

We report a 54-year-old, gravida 5, para 4, and postmenopausal woman with abnormal vaginal bleeding for 2 months. The patient's symptoms had worsened in the 2 weeks before the examination. The patient's surgical history included a total abdominal hysterectomy and right salpingo-oophorectomy because of uterine myoma for about 10 years ago, without any remarkable familial history of the disease.

The patient visited our gynecologic outpatient department for help with progressive vaginal bleeding. On gynecologic examination, there was a 1.0 cm × 1.0 cm × 0.8-cm raised, ulcerated, and irregular lesion over the anterior distant third vaginal wall (Fig. 1). On routine physical examination, there was no palpable bilateral inguinal lymph node. Biopsy of the vaginal wall proved the existence of a malignant melanoma in histopathological studies.

The patient received a major operation including total vaginectomy, radical vulvectomy, left salpingo-oophorectomy,

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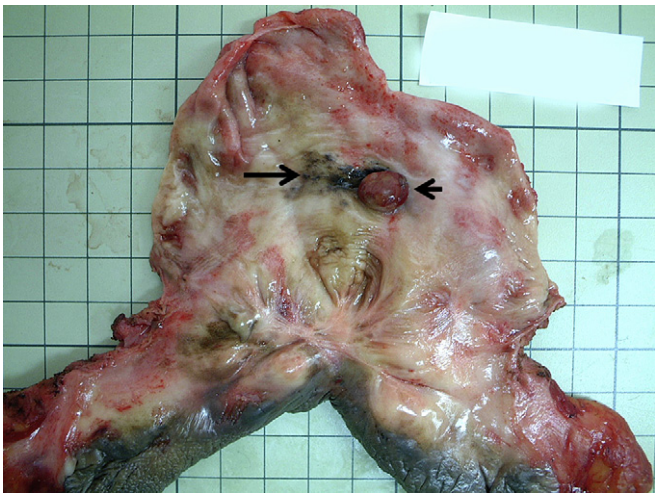

Fig. 1. Gross specimen of total vaginectomy and radical vulvectomy. A dark brown nodular lesion (short arrow), 1.0 cm × 1.0 cm × 0.8 cm, is identified in the vagina. Several irregular dark patches (long arrow) over the adjacent mucosa.

bilateral pelvic lymph node dissection, and bilateral inguinal lymph node dissection. Rotation of skin flap for perineum reconstruction had been performed after the radical surgery, but without neovaginal reconstruction. The tumor was superficial and displayed lentiginous spreading, with a Breslow depth of 9 mm, ulceration, and cytoplasmic melanin pigmentation. Pathologic reports described a nodular vaginal melanoma with clear margins, and all dissected lymph nodes displayed reactive hyperplasia. The histological diagnosis of the specimen was confirmed by positive human melanoma black 45 immunostaining. Based upon the revised tumor size, lymph node, and metastasis system staging of melanoma of the American Joint Committee on Cancer produced in 2009, the patient was staged IIc.[4]

The patient received postoperative immunotherapy with interferon-α-2b (IFNα-2b; F. Hoffmann, Switzerland) (15 MIU/m^2, intravenous, 5 d/wk) for 4 weeks. After the initial 4 weeks of IFNα-2b, the patient accepted the maintaining course of immunotherapy with IFNα-2b (12 MIU, subcutaneous, 3 times a week) for 4 months. Unfortunately, the patient received 3 excisions of recurrent vulvar, perineal, and rectal nodules on the 7^{th}, 9^{th}, and 15^{th} months after radical surgery, respectively. After the first and second excisions, she accepted C/T with Dacarbazine, dimethyl-triazeno imidazole-carboxamide (Hospira, Australia), 850 mg/m^2 every month for 6 courses. At last excision, she was given immunotherapy with IFNα-2b (12 MIU, subcutaneous, 5 days a week) and R/T 6100 cGy, 33 fractions over the perineum, for local control.

However, one month after the third excision, the patient suffered from slurred speech/facial palsy and complained of recurring headache, which began approximately two months before the operation. Magnetic resonance imaging of the brain revealed an intra-axial mass lesion about 3.0 cm × 2.6 cm × 2.8 cm at the left temporo-parietal junction. Metastatic melanoma was determined to be the most likely diagnosis. The patient underwent craniotomy and resection of the brain lesion. Histological examination proved that the patient had metastatic melanoma. After resection of the brain tumor, the patient accepted immunotherapy with IFN (12 MIU, subcutaneous, 5 days a week) and R/T 3000 cGy, 10 fractions over the whole brain, and 4500 cGy, 25 fractions over the whole pelvic and bilateral inguinal nodal regions. Later, the patient underwent repeated IFN and dimethyl-triazeno imidazole-carboxamide treatments, and resection of residual brain metastatic tumor. The patient is still alive, more than 30 months, after initial diagnosis (Fig. 2).

3. Discussion

Malignant melanoma of the vagina is very rare, accounting for 0.3–0.8% of all melanomas in women, 2–5% of female genital-tract melanomas, and less than 3% of vaginal tumors.[1] The tumor typically presents in the sixth and seventh decades of life and occurs more commonly in the lower third of the vagina and mostly on the anterior vaginal wall.[1,2] The appearance of tumors is almost always pigmented; only 10–23% are amelanotic.[5] The most common symptom is abnormal vaginal bleeding.[2]

This disease is associated with a high risk of local recurrence, distant metastasis, and poor clinical outcome. A retrospective review of vaginal melanoma disease by Michael et al revealed that the median survival of 37 cases in Stage I was 19.1 months.[2] Studies by Michael et al and Reid et al have shown that the tumor size and nodal status are significant prognostic factors, whereas tumor thickness is a weak predictor

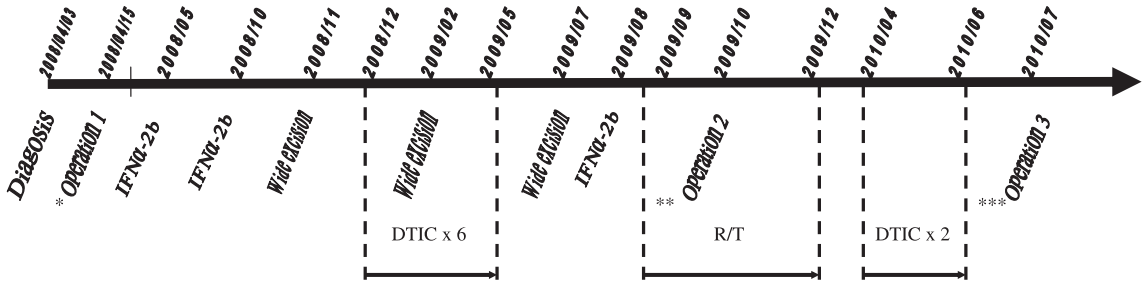

Fig. 2. The clinical courses of treatment, from 2008 to 2010.*Operation: total vaginectomy + radical vulvectomy + left salpingo-oophorectomy + bilateral pelvic lymph node dissection + bilateral inguinal lymph node dissection + rotation flap **Operation: left F-T-P craniotomy + removal of brain metastatic tumor ***Operation: left F-T-P craniotomy + removal of brain tumor Radiotherapy: 6100 cGy, 33 fractions over perineum; 3000 cGy, 10 fractions over whole brain; 4500 cGy, 25 fractions over whole pelvic and bilateral inguinal nodal regions.

Table 1
The summary of two clinical trials of Peg-IFN treatment on malignant melanoma

Study	No. of patients	TNM stage	IFN regimens	Arms: No. of patients	Outcome
Eggermont (EORTC 18991)[13]	1256	TanyN + M0 Stage III	Peg-IFN 6 μg/kg/wk for 8 wk (sc) then 3 μg/kg/wk for 5 y (sc)	Peg-IFN: 627 OBS: 629	4-year RFS rate Peg-IFN: 45.6% OBS: 38.9% $p = 0.02$
Bottomley[14]	1256	TanyN + M0 Stage III	Peg-IFN 6 μg/kg/wk for 8 wk (sc) then 3 μg/kg/wk for 5 y (sc)	Peg-IFN: 627 OBS: 629	Global HRQUL Peg-IFN is significantly lower than OBS $p < 0.004$

HRQUL = Health-related quality of life; IFN = interferon; OBS = Observation; Peg-IFN = pegylated IFNα-2b; RFS = recurrence free survival; TNM = tumor size, lymph node, and metastasis.

of survival.[2,6] To our best knowledge, there is no retrospective data regarding therapeutic options. Several treatment options are administered but none of them are considered to be a standard approach. Surgical resection is considered the first treatment of choice with survival benefit.[2,5] Different surgical methods such as wide local excision, radical surgery (total vaginectomy with or without vulvectomy), and pelvic exenteration have been described. However, research has continued to demonstrate that there is actually no difference in survival between patients who have radical surgical procedures and those who have more conservative surgical procedures.[3,5,7] Some authors suggest that radical surgery should be performed due to the more aggressive behavior of vagina melanoma.[8,9] After surgery, patients with a high risk of recurrence (including regional lymph node involvement or thicker primary tumors, i.e. American Joint Committee on Cancer Stage IIb/IIc/III) should be considered for adjuvant therapy.

Immunotherapy with IFN has been demonstrated to reduce recurrence rates and offer a survival advantage.[10,11] The Food and Drug Administration approved of high-dose IFN based on the results of a randomized Phase III trial (E1684).[10] IFN is the only drug approved by the Food and Drug Administration for adjuvant therapy in patients with malignant melanoma who are free of disease but at a high risk of systemic recurrence. An updated individual patient meta-analysis of 14 trials reported statistically significant improvement in both disease-free survival and overall survival in patients who received IFN.[12] Pegylated IFNα-2b (Peg-IFN), a derivative of recombinant IFN, does not compromise its effect and can be conveniently given once a week because of longer half-life. Peg-IFN has reduced toxicity, and toxicity does not seem to increase with longer duration of treatment. We reviewed two trials of Peg-IFN treatment on malignant melanoma, which are summarized in Table 1.[13,14] In the future, IL-2 and vaccine therapy may be the other options; however, they do not seem to improve the overall survival rate of patients with malignant melanoma.[15]

The role of cytotoxic C/T in vaginal melanoma has not been completely defined because of the small number of cases. Dacarbazine has been considered the standard of treatment for metastatic or recurrent melanoma since 1972. Other useful antineoplasm agents include temozolomide, platinum analogs, nitrosoureas, and taxanes. The response rate of these single agents is 11−22%, with median overall survival of 5.6−11 months. Combination C/T that is most commonly used for melanoma includes Dartmouth regimen (Dacarbazine/Carmustine/Cisplatin/Tamoxifen) and CVD regimen (Cisplatin/Vinblastine/Dacarbazine), which are proved to increase objective response rate but have no overall survival benefit.[16] Based upon the above observations, it may be possible to develop combination C/T regimens that improve overall survival in the future.

Some authors have considered biochemotherapy, a combination of C/T and immunotherapy, as a possible valid option after surgery to improve patient survival. Biochemotherapy is associated with higher response rates than other C/T regimens or immunotherapy for treatment of metastatic melanoma, but offers no survival benefit.[17]

The role of elective lymph node dissection remains controversial. Instead, sentinel lymph node biopsy (SLNB), which provides important prognostic and staging data with minimal morbidity, has recently gained popularity.[18] Routine lymph node dissection is not recommended because the morbidity associated with lymphadenectomy is high and prophylactic lymphadenectomy has not been shown to improve survival in vaginal melanoma.[4] Overall survival is significantly higher in patients who undergo SLNB and immediate lymphadenectomy compared with those who have lymphadenectomy only after having clinically detectable disease.[19] SLNB should be performed on most patients who have melanomas with a Breslow depth $\geq$0.76 mm.[18] However, in our case, the lymph nodes were dissected to provide for a complete staging of the tumor.

R/T also for local control has been mostly offered in the following two conditions, surgically non-resectable disease or as an adjuvant therapy in case of pathologically positive margins or positive lymphadenopathy.[2,5]

In conclusion, primary malignant melanoma of the vagina has poor prognosis at any stage, with high risk of local recurrence and distant metastasis. Surgical intervention seems to improve survival. After operation, adjuvant therapy should be considered for patients with a high-risk recurrence. In our case, repeated local excision followed by biochemotherapy/chemotherapy/radiation therapy was a tolerable treatment.

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