Case Report
Vaginal primary malignant melanoma complicating cervical carcinoma in situ: a case report and review of literature

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Abstract: Vaginal primary malignant melanoma (VPMM) is a rare and extremely aggressive tumor. Because of hidden location and lack of early symptoms, it usually develops at advanced stage and has very high mortality rate. Moreover, the etiology of this tumor is largely unknown. Therefore, it is important for improving prognosis to early diagnosis of VPMM. In the present study, we describe a 35-year-old female patient who was diagnosed as VPMM combined with CIN3 before any report not mentioned. The patient presented to our hospital with abnormal vaginal bleeding of 2 months. Preoperative colposcopic-directed biopsy and physical examination suggested malignant lesions occurred in the upper third of anterior vaginal wall. Then a wide local excision of the lesion was first performed. Postoperative pathological results confirmed and metastasis to left internal iliac lymphnodes. She underwent adjuvant radiotherapy and immunotherapy as further therapeutic measures. Although the patient could not complete a cycle due to intolerable toxicity of immunotherapy, she is still alive 14 months after diagnose.

Keywords: VPMM, etiology, treatment, surgery, radiotherapy

Introduction
Vaginal melanoma is a rare malignant tumor. It accounts for 2%-5% of all female genital tract melanomas, for less than 3% of all vaginal malignant tumors [1]. Cervical carcinoma in situ is a common kind of cervical intraepithelial neoplasia III (CIN3) level. However, VPMM complicated with CIN3 is a particularly rare event. There has been no relevant report. Here we report a case of VPMM with cervical carcinoma in situ and review the literature.

Case presentation
The patient, a 35-year-old female, Gravid 1 and Para 1, and previously had regular menstruation, menstrual cycle 30 days, period 5 days. She was admitted to local hospital with a complaint of abnormal vaginal bleeding for 2 months. Her previous and familial histories were unremarkable.

On pelvic examination, there was a lobulated, raised, part ulcerated, and irregular lesion 3×3 cm diameter in the upper third of anterior vaginal wall. There were no palpable lymph nodes, and the rest of pelvic and physical examination was normal. The patient was originally considered as vaginal tumor, thus the patient underwent colposcopy with lesion biopsy for diagnosis. Postoperative pathological results confirmed and metastasis to left internal iliac lymphnodes. She underwent adjuvant radiotherapy and immunotherapy as further therapeutic measures. Although the patient could not complete a cycle due to intolerable toxicity of immunotherapy, she is still alive 14 months after diagnose.

She underwent a wide hysterectomy, part vaginectomy, bilateral adnexitomy and pelvic lymphadenectomy. Pathological results showed plenty of atypical cells invading deep muscles with infiltrating cervical fornix, cervix labium anterius local squamous cell carcinoma in situ (Figure 1), left internal iliac lymph node was
involved, and without tumor tissue in the surgical margins and other lymph nodes. Immunohistochemical results indicated the tumorous cells were positive for HMB-45, S-100 protein, Melan-A, vimentin, Ki-67, and CK (Figure 2). The final diagnosis was VPMM and carcinoma in situ of cervix.

The patient received pelvic linear accelerator radiation, immunotherapy with interferon (IFN), intra-vaginal radiotherapy. But our patient did not tolerate immunotherapy on account of fever, so breaking off this therapy. She has multiple organ metastases and refuses further therapy 14 months of follow-up after diagnose.
Discussion

Malignant melanoma of the vagina is a rare cancer and its behavior is aggressive. There have been less than 300 VPMM cases reported worldwide up to now and accounts for less than 4% of all vaginal malignant tumors [2]. The incidence of VPMM is 0.46 cases per one million women per year [3]. The age of VPMM has been reported ranging from 22 to 90 years, with most commonly being diagnosed in post-menopausal period [4]. The overall 5-year survival rate for women with VPMM ranges from 0% to 25% [5]. It is primarily found in the lower third of vaginal wall [6], secondly located in mid-upper and total of vagina. Its symptoms commonly present as vaginal bleeding and discharge, mass lesion and less commonly dysuria or ulceration [7, 8]. Macroscopically it often presents like pigmented lesion. In present case, the lobulated and brown pigmented tumor is found in the upper of vagina, and mainly complaining of abnormal vaginal bleeding.

VPMM is one type of mucosal melanomas that stems from melanocytes and does not exposed to ultraviolet rays. Compared to cutaneous melanomas, mucosal melanomas are rare, and the risk factors have not been identified [9-11]. In recent study, a family history of melanoma was an important risk factor for mucosal melanomas [12]. Seifreid S deduced that cervical screening may lead to earlier diagnosis of vulvo-vaginal melanoma with exception of its primary aim [4]. Some reports [13, 14] verified that vulva melanoma links with HPV infection, and a case report found the positive of HPV6 and 11 with in situ hybridization (ISH) in benign melanosis lesions of the vagina which may be a precursor of malignant melanoma [15]. And Rohwedder et al. reported that cutaneous HPV and epidermodysplasia verruciformis (EV) could play a role in the pathogenesis of genital melanoma [13, 14]. The theory that HPV infection is necessary for progression to CIN-2/3 is to known [16, 17]. However, there is no clear whether HPV infection status is related to VPMM or CIN is associated with VPMM. We found two kinds of HPV infections (HPV33, 35) in our case.

It is of crucial importance for VPMM to early diagnose due to its appearing at an advanced stage and poor prognosis, with relation to its hidden location and the rich vascular [18-20]. Its diagnosis rely on pathological examination, typical melanoma that are commonly pigmented is easy to diagnose. However, amelanotic appearance is rare and makes diagnosis even more difficult [21]. Consequently, immunochemical staining should often be used to supplement the diagnosis, such as protein S-100, HMB-45, Melan-A, Mart-1 and vimentin. In our case, the pathological results only showed a malignant melanoma, and immunochemical analysis demonstrated HMB-45, S-100 protein, Melan-A and vimentin staining positive which further confirmed the diagnosis.

Although the management of the vaginal melanomas has many options including local wide excision, radical surgery, radiotherapy, chemotherapy and immunotherapy, the most effective treatment protocol has not reached consensus [22]. In these recommendations surgical resection remains the mainstay of melanoma and can improves OS, as compared with a primary radiotherapy [23]. Nevertheless, there has been controversial concerning surgical range, early studies advised radical surgery (vaginectomy and pelvic exenteration), but recent publications support conservative treatment (wide local excision) [24]. Tcheung WJ et al. [5] considered that conservative surgery can not only reduce local recurrence, but also decrease complication resulted from radical surgery.

On account of the rate of lymph node metastasis lower, the value of local lymph node dissection is not still certainty. Miner et al. [23] performed a systematic lymphadenectomy on 26 patients and found two lymph node metastasis. But we were to clear away if there should be suspicious lymph nodes during operation. The current case underwent lymph node dissection. Recently, the feasibility of the technique of the sentinel lymph node biopsy has been shown [25, 26]. Frumovitz et al. [27, 28] recommends its use.

Radiotherapy can be applied as adjuvant treatment for patients who are unable to surgery or who the surgery cannot completely remove or pelvic metastasis is possible. Our patient underwent a wide local excision, and received pelvic linear accelerator radiation and intra-vaginal radiotherapy.

Bio-immunotherapy is recently a new adjuvant treatment, and randomized clinical trial demon-
strate interferon (IFN) α2b is first medicine that is beneficial for advanced malignant melanoma, whose treatment can improve the total of survival time and disease-free survival time [29, 30]. However, toxicity is important [6, 31, 32]. In our patient, she did not receive immunotherapy due to fever. However, she is still alive 14 months after initial diagnosis.

In summary, Our patient illustrates that CIN3 could be a cause of VPMM or VPMM may bring about CIN3, via directly or indirectly oncogenic interactions, or as a cofactor, via activation of melanocytes, and whether VPMM be associated with HPV33 and 35 infections remains to be a further in-depth study.

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Disclosure of conflict of interest

None.

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