International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Primary Malignant Melanoma of the Uterine Cervix with S100 (Protein Marker Seen in Women with Melanoma) Negative Status and Novel ATM Gene Mutation: Case Report and Literature Review

Liang Wang

Department of Gynecology and Obstetrics, Tianjin NanKai Hospital, Tianjin, 300100, People's Republic of China

Correspondence: Liang Wang, Department of Gynecology and Obstetrics, Tianjin NanKai Hospital, No. 6 Changjiang Road, Nankai District, Tianjin, 300100, People's Republic of China, Tel +86-13802092719, Email liangwang0808@gmail.com

Abstract: Malignant melanoma (MM) is a relatively common malignant tumor. It mostly occurs in the skin, uvea of the eye, oral cavity, esophagus and anus, etc. Primary melanoma of the uterine cervix is very rare, with only more than 100 cases reported worldwide so far. In this article, we report a 42-year-old patient with primary cervical malignant melanoma. This case recorded the patient's entire process from onset, surgery, progression, treatment, deterioration, and death. The patient began to seek medical treatment after the discovery of cervical vegetations and eventually died of brain metastasis. The patient was negative for S100 by immunohistochemistry and had a frameshift mutation in the Ataxia-telangiectasia mutated (ATM) gene by genetic testing. This has never been described in previous cases and is reported for the first time.

Keywords: uterine cervix, malignant melanoma, S100 negative, ATM gene

Introduction

Malignant melanoma is a malignant tumor that occurs in the skin and mucous membranes, accounting for approximately 1% of all malignant tumors.[1] It mainly occurs in various parts of the mouth, esophagus, anus, uvea, skin, female reproductive organs, etc.[2] MM originating primarily in female reproductive organs are relatively rare, accounting for approximately 3–7%[3] of mucosal malignant melanomas, and mostly occur in the vulva and vagina.[4]

MM that occurs in the cervix is extremely rare, with only over 100 reported cases worldwide in more than 100 years of documentation.[5] The disease is extremely malignant. Due to its low incidence, poor treatment effect, and lack of systematic research, there is currently no worldwide diagnosis and treatment guideline or expert consensus.

At present, the main treatment method is still surgical treatment, including radical hysterectomy, total hysterectomy, lymphadenectomy and partial vaginectomy.[6,7] In this article, we report a 42-year-old patient with cervical MM and analyze previous literature.

Case Presentation

A 42-year-old patient presented with an abnormal vaginal discharge, and gynecologic examination revealed a cervical vegetation about 2 cm in diameter. The patient's preoperative Thinprep Cytologic Test (TCT) showed Atypical Squamous Cells, Cannot Exclude HSIL (ASC-H) and Human Papilloma Virus (HPV) showed negative, and no colposcopy was performed.

Received: 25 October 2024
Accepted: 27 March 2025
Published: 8 April 2025

As the patient had multiple uterine fibroids, laparoscopic total hysterectomy and bilateral salpingectomy were performed after consultation with her. As shown in Figures 1 and 2, intraoperative frozen pathology suggested that cervical neoplasm was malignant melanoma.

Since the preoperative Computed Tomography (CT) showed no lymph node metastasis and no involvement of the uterus, double adnexa, and vagina by cancer, no further lymph node and bilateral oophorectomy were performed after discussion with the patient's family.

Postoperative paraffin pathology confirmed cervical malignant melanoma. Immunohistochemistry: Vimentin (+), S100 (−), HMB45 (+), Melan A (+), CD3 (−), CD20 (−), CD99 (partially+), Ki67 (approximately 40%+); Leiomyoma Ki67 (approximately 3%+) (Figures 3 and 4).

The patient's malignant melanoma-prone areas such as skin, uvea, oral cavity and anus were examined, and no malignant melanoma was found. The patient was considered to have primary cervical malignant melanoma. According to the 2018 Federation International of Gynecology and Obstetrics (FIGO) cervical cancer staging, it is considered as stage IB2. Two months after the operation, the patient found a mass on the vaginal wall, which was 1 cm in size.

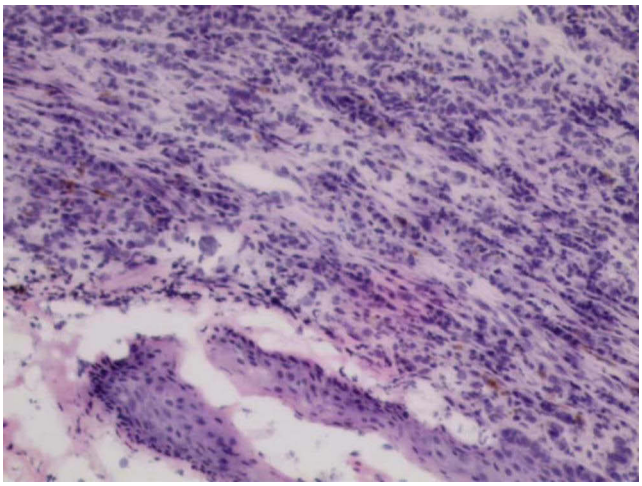

Figure 1 Intraoperative frozen pathology 100X magnification in a cervical neoplasm specimen.

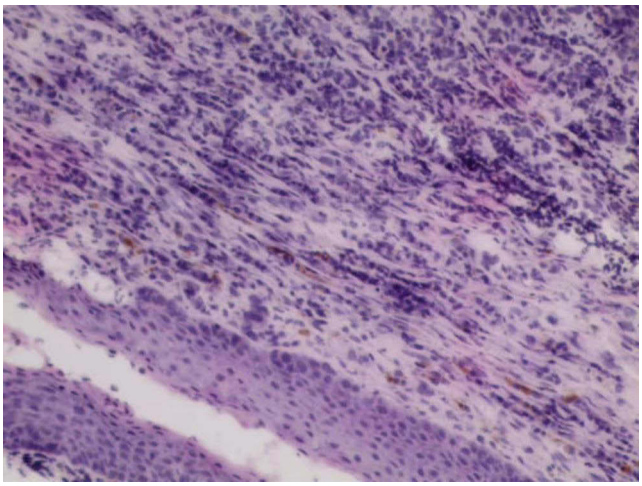

Figure 2 Intraoperative frozen pathology 100X magnification in another cervical neoplasm specimen.

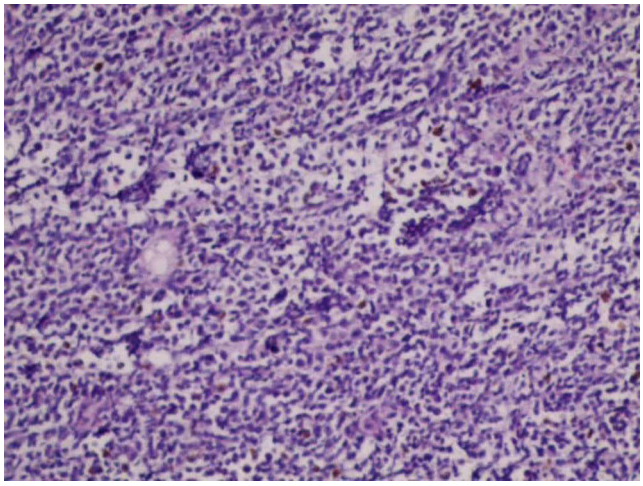

Figure 3 Hematoxylin-Eosin staining of postoperative paraffin pathology in the first surgery 100X magnification.

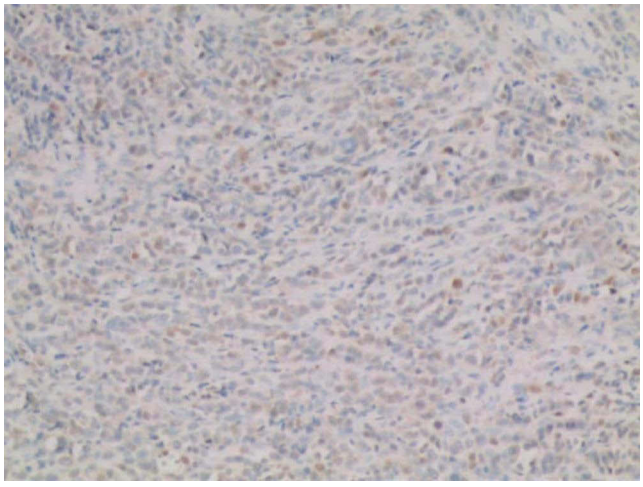

Figure 4 S100 negative in immunohistochemical staining of postoperative paraffin pathology in the first surgery 100X magnification.

Positron Emission Tomography-Computed Tomography (PET-CT) suggested that the soft tissue on the right side of the vagina was thickened and the metabolism was increased, so the tumor was considered to be recurrent. No tumor metastasis was found in the pelvic cavity and bilateral inguinal lymph nodes.

She was admitted to the hospital for treatment 3 months after surgery. On examination, a mass of about 2 cm in diameter was found on the right posterior wall of the vagina. Tumor resection was performed with the area around 3cm from the edge of the tumor as the resection range.

Immunohistochemistry was as follows (Figure 5): MelanA (+), HMB45 (+), Ki67 (approximately 80%+), CD99 (focal+). Considering the recurrence of malignant melanoma, regular intravenous infusion therapy with Toripalimab 240mg was initiated thereafter. Eight months after the first operation, ultrasound showed a hypoechoic mass (14.2*11.9*14.8mm) in the vaginal stump. At the same time, the patient discovered enlarged lymph nodes in the right inguinal region. B-ultrasound showed that the maximum lymph node size in the right inguinal region was about 3.06 * 1.24cm.

Pelvic magnetic resonance imaging (MRI) showed that there were multiple enlarged lymph nodes in the pelvic cavity and bilateral inguinal area and nodules in the vaginal stump (Figure 6). Recurrence and metastasis were considered. A puncture biopsy was performed, and the pathology suggested lymph node metastasis of malignant melanoma.

https://doi.org/10.2147/IJWH.S499393

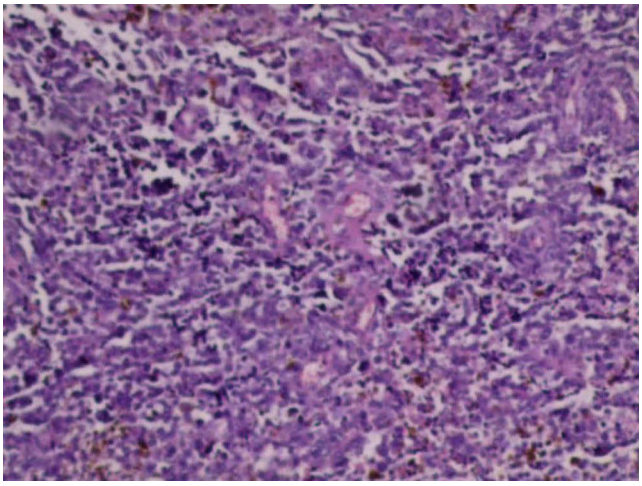

Figure 5 Hematoxylin-Eosin staining of postoperative paraffin pathology in the second surgery 100X magnification.

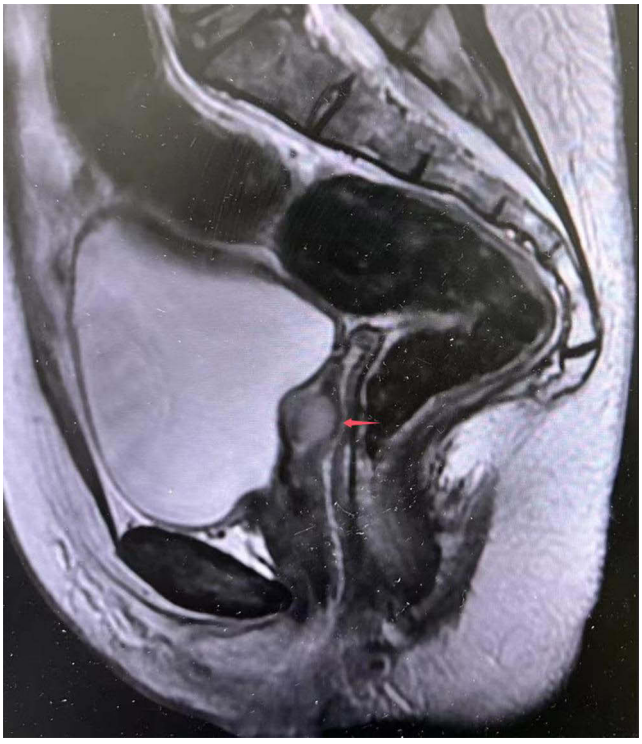

Figure 6 Pelvic MRI showed that there were multiple enlarged lymph nodes in the pelvic cavity and bilateral inguinal area, and nodules in the vaginal stump. The red arrow indicates the presence of nodules in the vaginal stump.

Immunohistochemical staining was as follows (Figures 7 and 8): Vimentin (+), HMB45 (+), Melan A (+), S-100 (partially+), p53 (not be excluded mutant type), LCA (corresponding+), CK pan (−), Ki-67 approximately 60–70%.

Since then, the patient had been receiving intravenous infusion treatment with toripalimab. Two months later, ultrasound showed that the right inguinal lymph nodes were significantly smaller than before. B-ultrasound showed that the largest lymph node in the right inguinal area was 1.79*0.49mm. After three months, the lymph nodes were no longer palpable, which proved that the treatment was effective. Ten months after the initial surgery, ultrasound examination revealed a hypoechoic mass (22.7 * 17 * 24.5mm) in the front of the vagina. Two weeks later, a follow-up ultrasound revealed a cystic and solid pelvic mass (49 * 28 * 41mm), and the mass was significantly larger than

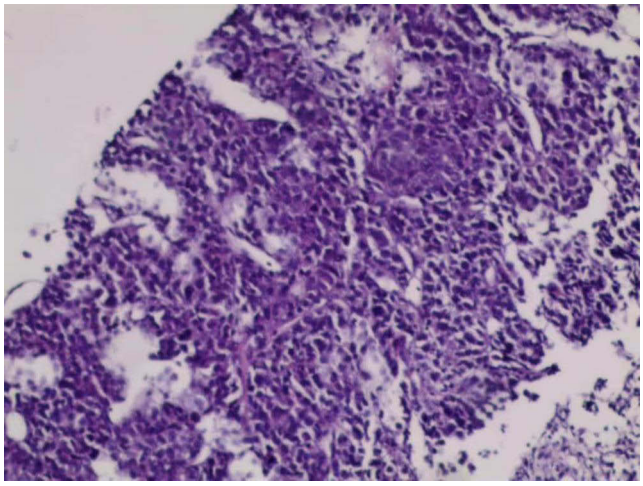

Figure 7 Hematoxylin-Eosin staining of the puncture biopsy 100X magnification.

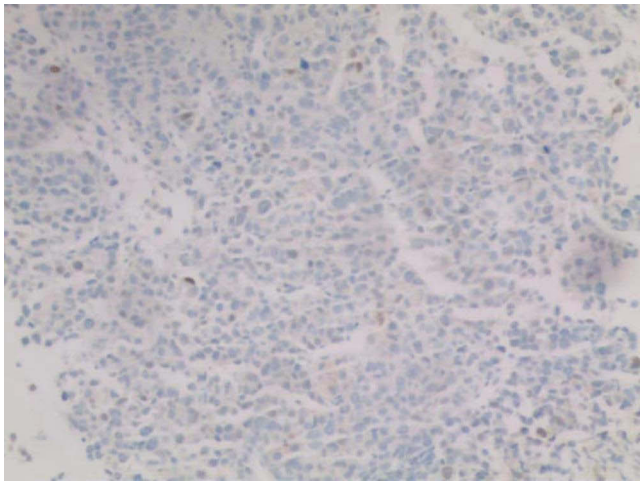

Figure 8 S100 partially positive in immunohistochemical staining of the puncture biopsy 100X magnification.

before. An ultrasound-guided aspiration biopsy of the mass was performed. Postoperative pathology showed that the size and morphology of tumor cells were more uniform, with increased nuclear plasma ratio and there was extrusion in some areas. Immunohistochemical staining as follows (Figures 9 and 10): Vimentin (+), HMB45 (+), Melan A (+), S-100 (+), p53 (not be excluded mutant type), LCA (corresponding+), CK pan (−), Ki-67, approximately 30–40%, which, in combination with medical history, was consistent with malignant melanoma.

One year after the operation, a follow-up ultrasound showed a cystic-solid occupancy above the vaginal stump, 50*29*44mm, and a solid occupancy in the left adnexal area, 42*33*38mm.

A pelvic MRI was performed more than one year after surgery. Compared with the MRI six months ago, the pelvic nodules and masses were more numerous and larger than before. The larger one was located on the left side of the pelvis and was about 3.9*4.7cm in size (Figure 11).

The patient started taking Axitinib 5mg twice a day orally for 2 months, and then underwent a follow-up ultrasound examination of a mass between the anterior part of the vagina and the bladder, which was 57.6 * 33.2 * 46.1mm in size. The left pelvic mass was 49.7 * 42.3 * 43.4mm, and the right pelvic mass was 35 * 25.4 * 34mm in size.

Considering the unsatisfactory effect, it was changed to Lenvatinib 8mg once a day. After 2 months of oral administration, a follow-up ultrasound examination showed that the mass between the front of the vagina and the bladder was 54.5*34.3*56.9mm, the left pelvic mass was 53.2*41.4*57.4mm, and the right pelvic mass was

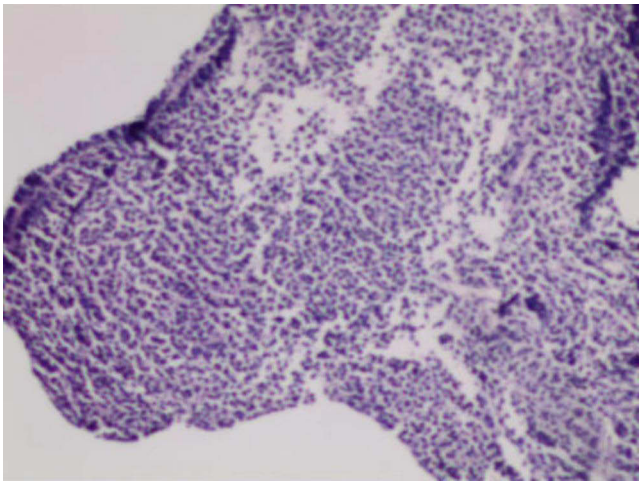

Figure 9 Hematoxylin-Eosin staining of the aspiration biopsy 100X magnification.

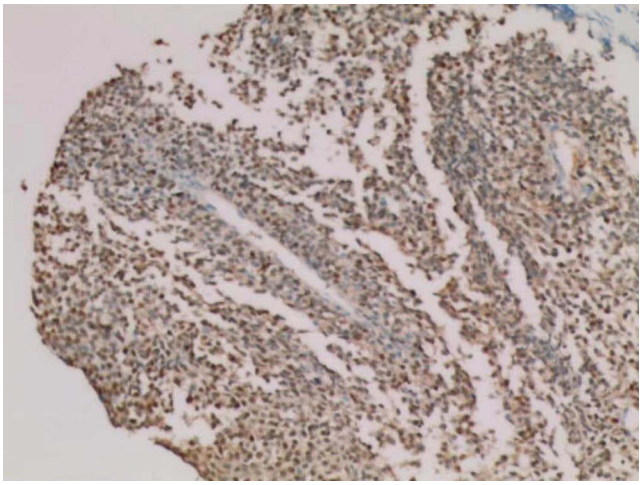

Figure 10 S100 positive in immunohistochemical staining of the aspiration biopsy 100X magnification.

45.5*32.6*41.7mm. The tumor was significantly larger than before, so oral administration of Lenvatinib was discontinued.

In February 2022, the pelvic MRI was repeated, and the nodules and masses in the pelvis were larger than before. The size of the mass on the left side of the pelvis was about 5.9*4.7cm (Figure 12).

No treatment was given from February to April 2022. The patient underwent genetic testing in March 2022. The results of peripheral blood genetic testing showed 7 somatic gene mutations and 1 germline mutation. The genetic testing results of paraffin-embedded sections of surgical tissues showed 3 somatic gene mutations, 2 gene copy number mutations, and 1 germline mutation. There was no overlap between somatic mutations in peripheral blood and paraffin sections, while the genetic susceptibility gene testing for tumors both showed ATM gene germline mutations.

The patient underwent a follow-up ultrasound in April 2022, which showed a solid mass above the vaginal stump, measuring approximately 73 * 54 * 79mm. Two solid masses were visible in the bilateral adnexal area, measuring approximately 64 * 48 * 63mm on the left side and 49 * 40 * 55mm on the right side. A solid mass could be seen in the left iliac fossa, about 36 * 23 * 30mm in size. No mass was found in the right iliac fossa. Compared with the ultrasound three months ago, the mass above the vaginal stump increased to three times its original size, the left pelvic mass

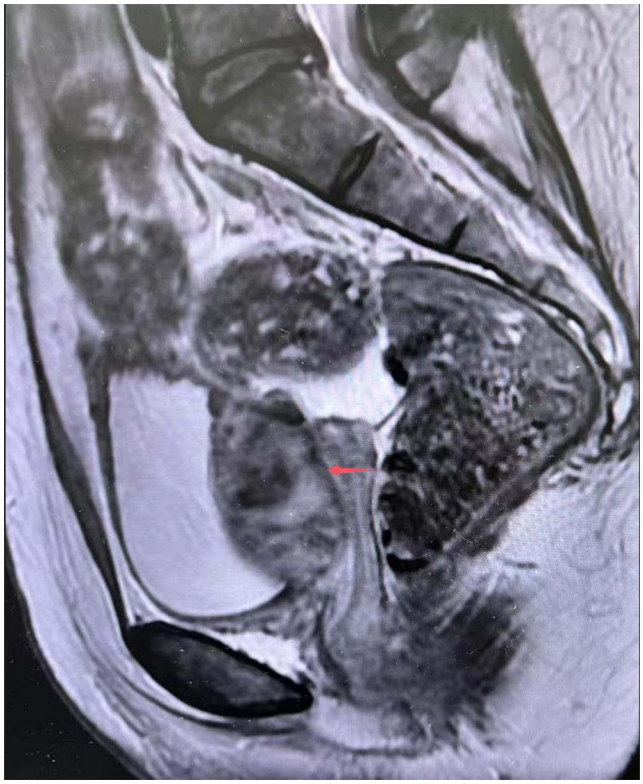

Figure 1 Pelvic MRI showed the pelvic nodules and masses were more numerous and larger compared with the MRI six months ago. The red arrow denotes a substantial enlargement of the residual nodule within the vaginal region.

increased to two times, the right pelvic mass increased to 1.3 times, and a new lump appeared in the left iliac fossa. Without any treatment, the tumor progression is significant. It showed that the tumor progressed significantly without any treatment.

Since April 2022, a combined treatment regimen of Toripalimab, Olaparib, and Lenvatinib will be administered. Toripalimab 240mg intravenous infusion, Olaparib 150mg twice a day, and Lenvatinib 8mg once a day oral administration. Among them, Toripalimab was intravenously administered every three weeks, while Olaparib and Lenvatinib were orally administered continuously every day without interruption.

Two months later, a follow-up ultrasound showed that, compared to the previous time, the mass above the vaginal stump had decreased to 6 times, the mass in the left pelvic cavity had decreased to 1.5 times, the lump in the right pelvic cavity had increased to 1.5 times, and the mass in the left iliac fossa had disappeared. The therapeutic effect was remarkable. Two months later, a follow-up ultrasound showed that the tumors above the vaginal stump and both sides of the pelvic cavity were slowly decreased in size compared to the previous period.

In the following six months, the mass above the vaginal stump had shrunk than before, while the bilateral pelvic tumors had significantly increased, and the treatment effect was not satisfactory.

Therefore, in January 2023, the patient adjusted the treatment regimen by discontinuing the intravenous infusion of Toripalimab and adding 100mg of temozolomide orally once a day. The plan was adjusted to temozolomide and Olaparib orally for 7 days, followed by 14 days of discontinuation before taking it again. Lenvatinib was orally administered daily without interruption.

After applying this plan for 3 cycles, the patient stopped taking temozolomide orally on March 18th and switched to daily oral administration of Olaparib and Lenvatinib. On April 3rd, the patient stopped taking oral Olaparib and Lenvatinib due to abdominal distension and stomach discomfort. On April 5th, the patient reported oliguria, facial and eyelid edema. On April 9th, the patient was hospitalized in the Gastroenterology Department of our hospital due to

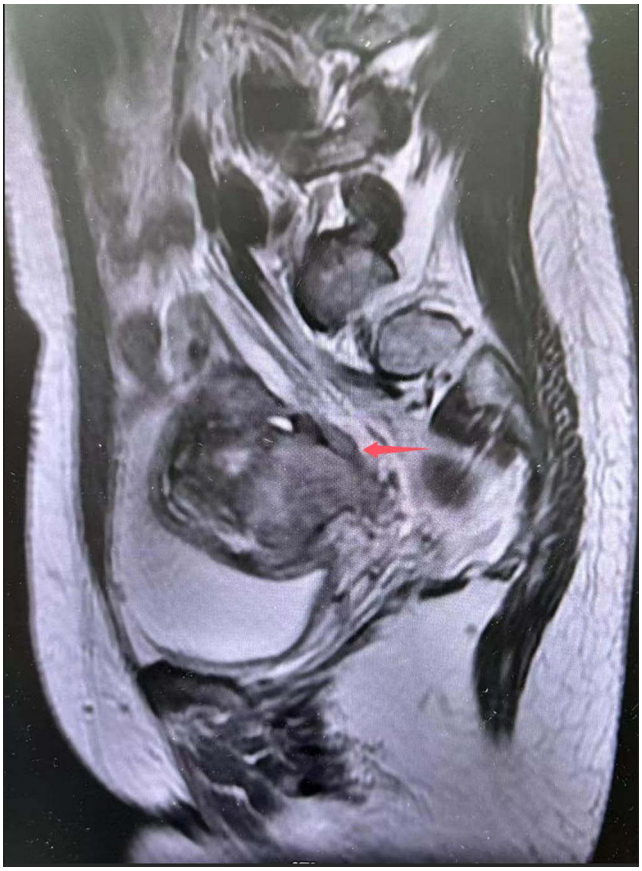

Figure 12 Pelvic MRI indicated that the nodules and masses in the pelvis were larger than before In February 2022. The red arrow denotes an increase in the size of the vaginal stump nodule relative to its dimensions in February 2022.

intermittent abdominal distension for two weeks. The abdominal ultrasound showed chronic liver damage, a hypoechoic mass in the body and tail of the pancreas, and abdominal and pelvic effusions.

After admission, the patient had oliguria and creatinine continued to rise, up to 370umol/L. Acute renal failure and hydronephrosis were considered, and a consultation with the urology department is requested. It was considered to be caused by tumor compression of the ureter.

The patient was transferred to the urology department and underwent bilateral nephrostomy on April 12th. After the fistula was done, she was transferred back to the gynecology department for further symptomatic treatment on April 18th. The patient's hemoglobin was 78g/L on admission and 47g/L when transferred to the gynecology department. Considering severe anemia, four units of suspended red blood cells were transfused intravenously to correct the anemia. She was discharged from hospital on May 1st. The patient was readmitted on May 2nd due to unconsciousness. She suddenly became unconscious and comatose 15 hours before admission, accompanied by involuntary tics in the right lower limb and occasional facial convulsions, which relieved in about 10 seconds. She was admitted to our department for brain metastasis of malignant melanoma.

An MRI scan of the head on May 2 revealed multiple metastatic masses and nodules in the intracranial brain parenchyma, accompanied by tumor hemorrhage and widespread peripheral edema. The anterior horn of the right ventricle was compressed and deformed, and there may be a herniation below the falx cerebri. On May 8th, the patient's hemoglobin was rechecked to be 58g/L. On May 9th, a large amount of dark red old blood was drained out through abdominal puncture, which was considered to be intra-abdominal hemorrhage. The patient died on May 11th.

Discussion

Incidence Rate

MM is a common malignant tumor, accounting for approximately 0.03% of all newly diagnosed cancers worldwide.[8] It often occurs in the skin and mucous membranes, and malignant melanoma originating primarily in the female reproductive tract is relatively rare. Melanoma of the female genital tract mostly occurs in the vulva and vagina,[9] and it is extremely rare to originate in the cervix.[6]

Since the first case of cervical malignant melanoma was reported in 1889, only over 100 cases had been reported worldwide to date. According to reported cases, patients with primary malignant melanoma of the cervix spanned a wide age range, with a known minimum age of 19 years and a maximum age of 83 years, and the peak age of onset was between 60 and 70 years old.[10–12] A recent review showed that the average age at diagnosis was 58 years old.[5]

Etiology

In the past, it was generally believed that there were no melanocytes in the cervix and therefore all cervical malignant melanomas should be metastatic from other parts of the body.

It was not until 1959 that Cid discovered that 3.5% of cervical specimens contained melanocytes,[13] and cases of benign cervical nevi were reported.[14,15] Since then, primary cervical malignant melanoma had been widely accepted by the general public. Cervical melanocytes may migrate from the neural crest or differentiate into melanocytes from the cervical epithelium, and then undergo malignant transformation.[2,16] These melanocyte precursors migrate from the neural crest and may migrate to the cervix under some unknown circumstances.[17]

At present, the mechanism of primary cervical malignant melanoma is still unclear, and skin malignant melanoma is mostly related to exposure to ultraviolet rays, psoralen and UVA (PUVA) therapy, and use of tanning salons.[18] Due to the particularity of its location, cervical MM excludes the factor of ultraviolet radiation, and no clear and conclusive susceptibility factors have yet been found.[19] Some literature suggests that it is related to factors such as genetic susceptibility, infection, and microenvironment.[20]

There were also studies suggesting that the occurrence of MM may be related to a high estrogen state.[21] However, according to previous reports in the literature, cervical MM often occurred in postmenopausal elderly people aged 50–70 years old,[3,19,22] who had relatively low levels of estrogen. Rohwedder et al showed that the primary MM of the cervix was associated with HPV infection,[23] as HPV16 subtype infection had been found in vulvar malignant melanoma, it was believed that HPV virus may promote the development of the disease.

But currently, the infection rate of HPV is relatively high among women in the general population, whereas the incidence of cervical MM is extremely low. Benson et al reported a case of cervical squamous cell carcinoma patients who underwent radiotherapy leading to cervical MM,[24] suggesting that radiotherapy may also be a risk factor for cervical MM. There was also a case report of cervical MM in postpartum women, suggesting that immunosuppression during pregnancy may also be a risk factor for MM and be related to the occurrence of malignant melanoma.[25] Although most cutaneous melanomas are closely related to gene mutations such as NRAS and BRAF, no closely related genetic alterations have been found in cervical malignant melanoma.[25,26]

The ataxia–telangiectasia mutated (ATM) gene is frequently identified as an aberrant gene in sporadic malignant tumors. Studies have demonstrated the presence of ATM mutations in the tumor cells of various cancers, including breast, gastric, bladder, pancreatic, lung, and ovarian cancers, often correlating with a poor prognosis. The inactivation of ATM markedly enhances the sensitivity of patients to radiation therapy, augments genomic instability, and accelerates cellular apoptosis.[27]

In this case, the patient's genetic test results showed a frameshift mutation in the ATM gene. It had been reported that the ATM gene had a moderate correlation with malignant melanoma.[28] However, it was the first time that a germline mutation of the ATM gene had been found in cervical malignant melanoma.

Clinical Manifestations, Diagnosis, and Staging

The initial symptoms of primary cervical malignant melanoma are mostly vaginal bleeding, discharge, as well as difficulty in sexual intercourse, and bleeding after intercourse.[29,30] These symptoms are not specific, and therefore it is difficult to make a correct diagnosis.

Gynecologic examination reveals cervical vegetations, which ranged in diameter from 0.5 to 7 cm and involved the vaginal fornix in more than 50% of cases.[10] Tumors can appear black, brown, blue, or red, and even non-pigmented. The microscopic manifestation shows spindle-shaped cells with large, deeply stained nuclei containing melanin.

In some cases, MM cells may not contain melanin, and it has been reported in the literature that tumors can be amelanotic in approximately 45% of cases.[31] However, amelanotic tumors also bring difficulties to the diagnosis of MM. Because this disease is rare and the tumor morphology is diverse, it is prone to misdiagnosis. Before diagnosis, the possibility of lymphoma, soft tissue sarcoma, poorly differentiated squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma should be excluded.[32]

Diagnosis is usually confirmed on the basis of gynecological examination, colposcopy, histopathological examination and immunohistochemical staining.[3] Immunohistochemistry is required to confirm the diagnosis because of the diversity of tumor manifestations and the absence of intracellular melanin.[32,33] The immunohistochemical staining of primary cervical malignant melanoma is usually negative for cytokeratin and positive for S100, Melan A, HMB45, MART1, and vimentin.[2,34,35]

S100 is a neural-specific protein that is most commonly found in nervous system cells, such as nerve cells (called neurons) and supporting cells (called glial cells and Schwann cells). It also exists in immune system cells such as dendritic cells, melanocytes, adipocytes, cartilage, and salivary glands. It is a biomarker for neurogenic tumors such as schwannoma and neurofibroma and can also be expressed in malignant melanoma and some mesenchymal malignancies. Therefore, s100 is one of the commonly used antibodies in pathological immunohistochemical diagnosis. HMB45 is a glycoprotein associated with the maturation of melanosomes from stage I to stage II. In normal tissues, HMB45 can be expressed in retinal pigment epithelium and fetal melanocytes, but it is not expressed in mature melanocytes or intradermal nevi. HMB45 is a biomarker for melanocytic tumors and tumors with melanin differentiation.

S100 protein has high sensitivity, HMB45 protein has high specificity, and the combined use of the two markers improves the accuracy of MM diagnosis.[31] From previous reports in the literature, almost all primary and 96% of secondary melanomas are positive for S100.[36–38]

In this article, the cervical neoplasms were confirmed to be cervical malignant MM by histopathology and immunohistochemistry. Its immunohistochemistry was positive for HMB45, Melan A, and vimentin, but negative for S100. This had never been reported in the previous literature.

In recent years, there had also been reports on the diagnosis of malignant melanoma by cervical cytology. For example, Deshpande et al reported a case of primary cervical malignant melanoma diagnosed by cervical scraping cytology.[31] Liquid-based cytology could also assist in the diagnosis of cervical malignant melanoma. According to literature reports, some scholars had successfully applied cervical liquid-based cytology in the diagnosis of cervical MM for the first time, even though it was a metastatic lesion.[39] In addition, Gupta et al reported that fine needle aspiration cytology could also be used to diagnose cervical melanoma.[40]

In this article, we reported a case in which preoperative cervical TCT showed HSIL and HPV was negative. Although TCT did not directly indicate malignant melanoma, it provided new clues and ideas for the diagnosis of cervical MM in the future. In this case, when melanoma metastasis in lymph nodes and vaginal stump was considered, fine-needle aspiration biopsy was used to confirm it.

When melanoma was first discovered in this patient, S100 was negative. During lymph node biopsy, S100 was partially positive, while during vaginal stump biopsy, S100 was positive. This indicated that as malignant melanoma progressed and metastasized, S100 underwent a change from negative to positive, which was also the first time it had been discovered and reported.

MRI is also valuable in defining the extent of cervical MM involvement. MM shows high signal intensity on T1-weighted images and low signal intensity on T2, which can distinguish melanoma from other tumors.[2,41] After the

diagnosis of cervical MM is made, it is also necessary to distinguish whether the MM is primary or secondary. The four diagnostic criteria for primary cervical malignant melanoma were summarized by Norris et al[42] as early as 1966. There were pigments present in the normal cervical epithelium around the tumor. No melanoma in other parts of the body. The migration process of lesions in the cervix. Consistent with the metastasis pattern of cervical cancer. According to previous case reports and literature, a considerable number of cases did not fully meet the above four criteria. Before diagnosing primary cervical MM, it is necessary to carefully examine the patient's uvea, oral cavity, esophagus, anus, and other parts to rule out the possibility of metastatic tumors.[3]

However, the cervical fibrous stroma is hard and the blood supply is not rich, which does not provide the optimal conditions for tumor metastasis.[39,43] In this case, after examination of the oral cavity, esophagus, anus, and uvea, no MM was found, and she was confirmed to be the primary cervical MM.

Previous literature had reported that cervical MM could spread to the vaginal fornix, uterosacral ligaments, parametrial tissues, vulva, and even to the pelvic wall. It was less common to extend to the uterine body.[31,44] If the vaginal wall was involved, there was an increased likelihood of inguinal lymph node involvement.

Cervical MM tends to progress locally[6] and distant metastasis is less common. It can develop rapidly or may remain dormant for several years. The most common sites of metastasis are the vagina, vulva, or near suture lines,[31] while common distant metastasis sites are lungs, liver, bones, and intestines, and even the brain. Pusceddu et al reported that the most common sites of metastasis were liver, peritoneum, and bladder. Noguchi et al reported a case of pulmonary recurrence after treatment.[45]

After total hysterectomy in this patient, the melanoma first metastasized to the anterior wall of the vagina, then metastasized to the inguinal lymph nodes, then metastatic tumors were found above the vaginal stump, and then in the left and right pelvic cavities. The tumor gradually increases, ultimately leading to ureteral compression, hydronephrosis, and renal failure. Multiple metastatic lesions can also be seen in intra-abdominal organs such as the liver and pancreas, leading to intra-abdominal hemorrhage, hemoperitoneum, and ultimately brain metastases and cerebral hernia, leading to the death of the patient.

This patient first experienced metastasis to the anterior wall of the vagina, then to the inguinal lymph nodes, followed by tumor metastasis over the vaginal stump and in the right and left pelvis.

During a period of more than two years, the tumor was confined to the pelvic cavity without significant distant metastasis, indicating that the characteristics of cervical MM, as described in previous literature, are more prone to local progression. Within a fixed period of time, the tumor is more like dormant, without rapid progression and distant metastasis. Once the tumor awakens for some reasons, such as discontinuation of medication or replacement with other ineffective drugs, the tumor can rapidly progress within a month or two, leading to distant metastasis and even brain metastasis, resulting in patient death.

At present, the Bre staging system for MM is differentiated based on the thickness of the tumor, which is related to prognosis.[2,22] The Clark and Breslow scales are commonly used for melanoma. However, the metastasis pathway of cervical malignant melanoma is similar to that of cervical cancer. Currently, FIGO cervical cancer staging is more preferred, as it has a better correlation with prognosis.[1,10]

Treatment and Prognosis

Due to the extreme rarity and low incidence of cervical MM, there is currently a lack of international diagnostic and therapeutic guidelines and consensus, and up to now, only one guideline on the diagnosis and treatment of primary cervical malignant melanoma has been published in China.[46]

The most common treatment currently is surgery.[41,44,47] It may be supplemented with chemotherapy, radiotherapy and immunotherapy. The first recommended surgical treatment is radical hysterectomy.[47–50] Depending on the situation, pelvic lymph node resection and partial vaginectomy may be performed simultaneously.[6,43,51]

Some scholars believe that due to the poor prognosis of this disease, more conservative surgical methods such as palliative local resection surgery can be used for large in volume, unresectable melanomas.[24,47,52] Previously, there was controversy over whether to perform radical hysterectomy or total hysterectomy, and currently radical hysterectomy had been widely accepted.

Some recent studies had shown that patients who underwent radical hysterectomy had a longer survival period than those who underwent total hysterectomy.[5,53] Regarding the issue of lymph node removal, there was still some controversy before. Jones et al found that 30% of lymph nodes with normal appearance had microscopic melanoma metastases,[47] so routine regional lymphadenectomy was recommended. Kristiansen believed that routine lymphadenectomy was not effective in improving prognosis, and its effectiveness in staging and treatment of melanoma was still controversial.[51,52]

If enlarged para-aortic lymph nodes were found or the tumor extended beyond the uterus, para-aortic lymphadenectomy may also be performed.[34,51] Currently, an increasing number of studies had found that patients undergoing lymphadenectomy had a longer survival period.[5,53] Regarding vaginectomy, since most patients with vaginal metastasis also have extensive metastasis to other parts of the body, partial vaginal resection or local tumor resection is more acceptable than extensive vaginectomy. But if the vaginal wall is involved, the inguinal lymph nodes may also be involved.

In this case, the patient underwent laparoscopic total hysterectomy, and recurrence of melanoma lesions was found on the anterior vaginal wall over one month after the operation.

If the patient had previously undergone radical hysterectomy, in the surgery, she received a resection of 2–3cm of vaginal wall tissue in addition to removing part of the parametrial tissue, and thus the possibility of vaginal wall recurrence would be reduced accordingly.

After the recurrence of tumor on the anterior wall of the vagina was found, tumor resection was performed with the area around 3cm from the edge of the tumor as the resection range.

Postoperative pathology suggested that the vaginal mass was malignant melanoma, and the tumor was visible at the local resection margin.

It means that the resection area of 3 cm from the edge of the tumor is not enough, and if vaginal metastasis is considered, the resection range should be expanded or total vaginectomy should be performed. Chemotherapy is generally used mostly for skin MM. There is currently no ideal chemotherapy regimen for cervical MM. Dacarbazine is the most widely used drug and may have a role in the treatment of cervical MM,[52] but the effective rate is only 15–20%.[54,55]

There was no significant survival benefit from previous chemotherapy treatment for primary cervical MM.[56] Cervical MM is a radioresistant tumor, and the therapeutic effect of radiotherapy is not good. It is generally used in adjuvant, preoperative, and palliative treatments.[41] Adjuvant pelvic radiotherapy can be applied to patients with unsatisfactory surgical resection, parametrial infiltration, and lymph node positivity.[3,57]

Immunotherapy had developed rapidly in recent years. Since 2011, a variety of immunotherapies had been used for malignant melanoma, such as anti-CTLA-4 antibody ipilimumab, anti-PD-1 antibodies nivolumab and pembrolizumab, vemurafenib and dabrafenib targeting BRAF mutations, imatinib targeting KIT mutations and MEK1, MEK2 inhibitor trametinib, etc. Ipilimumab, an immune checkpoint inhibitor targeting CTLA-4, had been shown in studies to improve survival in metastatic melanoma.[58,59] Imatinib and trametinib have also shown good effects in advanced melanoma.[60,61]

Studies had shown that compared with ipilimumab, pembrolizumab prolongs progression-free survival and overall survival in patients with advanced malignant melanoma without significant increase in toxicity.[62–65]

However, most of these studies were focused on malignant melanomas such as skin, and there were fewer studies on malignant melanomas of the female genital tract. In recent years, there have been some reports on the use of Programmed Cell Death Protein 1 (PD-1)/Programmed Cell Death-Ligand 1 (PD-L1) inhibitors such as pembrolizumab to treat cervical malignant melanoma,[8,66] but the treatment effect is not satisfactory, which is speculated to be related to the treatment of cervical PD-L1 negative cases.

BRAFV600 mutations had been found in approximately 50% of melanoma.[67] The drugs dabrafenib and vemurafenib targeting this mutation had been used in patients with advanced malignant melanomas and have shown good results.[68,69] However, cervical MM belongs to mucosal MM, which is different from skin MM. The BRAF mutation rate is lower in mucosal MM, so drugs targeting BRAF mutations are less effective.

In this case, this patient began to receive intravenous infusion of Toripalimab once every two weeks 4 months after the operation. One year after surgery, the patient started taking 5mg of Axitinib orally twice a day, and after 2 months of oral administration, she switched to imported Lenvatinib 8mg once a day, and then discontinued due to ineffectiveness.

The patient stopped all medications on her own more than a year after surgery, and there was no treatment during the two months period from February to April 2022. The ultrasound was reviewed in April. Compared with the ultrasound 3 months ago, the tumor progressed significantly. The combination therapy of Toripalimab, Olaparib, and Lenvatinib was administered from April. Two months later, follow-up ultrasound showed significant tumor reduction compared to the previous one, and the treatment effect was significant.

The ultrasound was reviewed again 2 months later, and the tumors were smaller than before, but the rate of reduction slowed down. In the following six months, except for the shrinking of the tumor above the vaginal stump compared to before, the bilateral pelvic tumors have significantly increased than before, indicating that the treatment effect was poor. As a result, the patient's treatment regimen was adjusted by discontinuing the intravenous infusion of Toripalimab and replacing it with oral administration of temozolomide 100mg once a day.

But the treatment effect was not satisfactory, the tumor continued to progress and enlarge, and symptoms of oliguria, facial and eyelid edema appeared. By April, the patient was readmitted to the hospital for treatment due to obvious abdominal distension, and all treatment drugs were stopped. Throughout the entire treatment process of the patient, the combined treatment regimen of Toripalimab, Olaparib, and Lenvatinib had a significant therapeutic effect within the first two months, with the tumor significantly shrinking compared with before, and in the following two months, although the treatment was effective, the rate of tumor shrinkage significantly slowed down.

Since then, the tumor increased significantly, and the treatment effect was poor. Overall, if more effective targeted drugs were used, the tumor could enter a dormant phase, with reduced tumor volume or slow progression.

However, it is more difficult to prolong this dormancy period because effective targeted drugs may become ineffective after 3–4 months of application, leading to tumor enlargement and progression. At this time, it becomes tricky to seek a switch to a different targeted drug. Upon investigation, it is possible that the development of tumors is influenced by multiple mechanisms and pathways, and targeted drugs may inhibit one or several of them, while other mechanisms and pathways may have substitutive and compensatory effects after these are inhibited, leading to a decrease in the effectiveness of targeted drugs.

If multiple targeted drugs that cover its mechanisms and pathways can be found and used in combination, it is expected to effectively control the progression of tumors. The prognosis of primary cervical MM is very poor, with survival period ranging from a minimum of a few days to a maximum of 14 years.[41] The median overall survival period is 12 months, and most of them die in three years after diagnosis. In one study of 78 patients, only two patients survived longer than 5 years.[6]

From the time, the patient was diagnosed with malignant melanoma after surgery in September 2020 to his death in May 2023, the patient's survival period was about 2 years and 8 months, less than 3 years, which is consistent with previous literature descriptions. The period of 2 years and 8 months was divided into 4 stages. The period from September 2020 to February 2022 is a slow progression period of the disease. This period starts from the onset of postoperative melanoma metastasis on the vaginal wall to the slow increase of melanoma metastasis above the vaginal stump and in the left and right pelvic cavities.

From February to April 2022, there was a period of rapid progression. In this period, the melanoma metastasis lesions rapidly increased above the vaginal stump and in the left and right pelvic cavities, and tumor metastasis appeared in the left iliac fossa. The period from April 2022 to March 2023 was a slow progression period. From April to June, the tumor shrank rapidly and the disease was effectively controlled. From June to August, the tumor shrinkage slowed down. From August 2022 to March 2023, the tumors in the left and right pelvic cavities slowly increased.

The medication was discontinued in early April 2023, and within a month, the disease entered a period of rapid progression with extensive and multiple intra-abdominal metastases, intra-abdominal hemorrhage, and then death of the patient with brain metastasis.

Conclusion

Reviewing the case, the gynecological examination of the patient revealed a cervical neoplasm of about 2cm in diameter. TCT showed ASC-H. Routine colposcopy should be performed, and the neoplasm should be removed for pathological examination. The next step of treatment should be carried out after the pathological results were available. If the pathological results indicated malignant melanoma of the cervix, radical hysterectomy and pelvic lymph node dissection should be performed routinely. If laparoscopic total hysterectomy was performed directly, the extent of the resection was insufficient.

The patient's cervical vegetations were considered to be malignant melanoma. The gynecological examination found no vaginal metastases, only local lesions on the cervix. Two months after laparoscopic total hysterectomy, a vaginal wall mass was discovered in the patient, and PET-CT suggested tumor recurrence.

From this perspective, on the one hand, it is necessary to carefully examine whether there are lesions in the anterior and posterior fornix and vaginal wall. On the other hand, even if there were no missed metastatic lesions, a portion of the vaginal wall tissue proximal to the cervix should be resected, as it could not be determined whether there were microscopic lesions. Therefore, the survival rate of patients undergoing extensive hysterectomy was significantly higher than that of other patients, which may also be related to the removal of part of the vaginal tissue in addition to the removal of part of the parametrial tissue. PET-CT showed no signs of pelvic lymph node metastasis 2 months after surgery. Eight months after surgery, it was found that the right inguinal lymph nodes were enlarged. The pelvic MRI showed multiple enlarged lymph nodes in the pelvic and bilateral inguinal areas. Metastases were first examined.

In this case, the patient first developed vaginal metastasis, and six months later, there were lymph node metastases in the groin and pelvic cavity. Because the CT scan showed no lymph node metastasis before the patient underwent laparoscopic hysterectomy, no lymph node dissection was performed. Therefore, it was recommended that patients underwent routine pelvic lymphadenectomy regardless of whether lymph node metastasis was detected, and if necessary, inguinal lymph node resection could be performed. The survival rate of patients who underwent lymphadenectomy was higher than that of other patients, which may also be related to this.

Genetic testing facilitates the identification of gene mutations linked to chemotherapy and immunotherapy, thereby allowing patients to select more appropriate targeted therapies and evaluate the risk of tumor recurrence and prognosis. Nevertheless, given the exceedingly low incidence rate of certain rare tumors and the absence of identifiable target genes, it is improbable to identify sensitive chemotherapeutic and targeted drugs through genetic testing.

In this article, we reported a case of cervical malignant melanoma, which had the following three characteristics. First, the immunohistochemistry was negative for S100 at the beginning and then partially and completely positive for S100 on re-biopsy. This has not been found in previous reports. Second, the discovery of germline mutations in the ATM gene in cervical malignant melanoma was the first report. Third, a complete process of onset, treatment, progression, and death was documented.

The process of this disease had gone through a period of dormancy, awakening, and rapid development, proving that the onset of cervical malignant melanoma was neither uniform nor accelerated, and it had a relatively stable dormancy period. Once awakened, the disease progression would be accelerated.

In summary, primary cervical malignant melanoma is extremely rare and highly malignant, and there are currently no international guidelines for diagnosis and treatment. The first recommended treatment option is radical hysterectomy and pelvic lymphadenectomy. Depending on vaginal involvement, partial or complete vaginectomy may be performed. Since vaginal involvement may be accompanied by inguinal lymph node involvement, inguinal lymph node dissection may be feasible depending on the situation. Postoperative chemotherapy, radiotherapy, and immunotherapy may be considered as additional options.

Abbreviations

ATM, Ataxia-telangiectasia mutated; MM, Malignant melanoma; TCT, Thinprep Cytologic Test; ASC-H, Atypical Squamous Cells, Cannot Exclude HSIL; HPV, Human Papilloma Virus; CT, Computed Tomography; FIGO, Federation International of Gynecology and Obstetrics; PET-CT, Positron Emission Tomography-Computed

Tomography; MRI, magnetic resonance imaging; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Cell Death-Ligand 1.

Ethics Statement

Written informed consent for publication of the case details and accompanying images was obtained from the patient's next of kin. No need for institutional approval to publish the case details and accompanying images.

Disclosure

The author reports no competing interests in this work.

References

1. Morrow CP, DiSaia PJ. Malignant melanoma of the female genitalia: a clinical analysis. *Obstet Gynecol Surv*. 1976;31(4):233–271. doi:10.1097/00006254-197604000-00001
2. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol*. 2007;56(5):828–834. doi:10.1016/j.jaad.2006.06.017
3. Piura B. Management of primary melanoma of the female urogenital tract. *Lancet Oncol*. 2008;9(10):973–981. doi:10.1016/S1470-2045(08)70254-7
4. DeMatos P, Tyler D, Seigler HF. Mucosal melanoma of the female genitalia: a clinicopathologic study of forty-three cases at Duke University Medical Center. *Surgery*. 1998;124(1):38–48. doi:10.1016/S0039-6060(98)70073-X
5. Min A, Fu A, Huang M, et al. Primary malignant melanoma of the cervix: an integrated analysis of case reports and series. *Front Oncol*. 2022;12:913964. doi:10.3389/fonc.2022.913964
6. Pusceddu S, Bajetta E, Carcangiu ML, et al. A literature overview of primary cervical malignant melanoma: an exceedingly rare cancer. *Crit Rev Oncol Hematol*. 2012;81(2):185–195. doi:10.1016/j.critrevonc.2011.03.008
7. Min KJ, Kim Y-S, Hong J-H, et al. Primary malignant melanoma of uterine cervix: a suggestion of new scheme of treatment combination. *Chin J Cancer Res*. 2014;26(3):351–354. doi:10.3978/j.issn.1000-9604.2014.06.03
8. Kim MS, Choi C-H, Kim T-J, et al. Primary malignant melanoma of the uterine cervix treated with pembrolizumab after radical surgery: a case report and literature review. *Obstet Gynecol Sci*. 2018;61(4):524–528. doi:10.5468/ogs.2018.61.4.524
9. Yücesoy G, Kus E, Cakiroglu Y, et al. Primary malignant melanoma of the cervix: report of a case. *Arch Gynecol Obstet*. 2009;279(4):573–575. doi:10.1007/s00404-008-0761-x
10. Mordel N, Mor-Yosef S, Ben-Baruch N, et al. Malignant melanoma of the uterine cervix: case report and review of the literature. *Gynecol Oncol*. 1989;32(3):375–380. doi:10.1016/0090-8258(89)90645-8
11. Clark KC, Butz WR, Hapke MR. Primary malignant melanoma of the uterine cervix: case report with world literature review. *Int J Gynecol Pathol*. 1999;18(3):265–273. doi:10.1097/00004347-199907000-00013
12. Gupta R, Singh S, Mandal AK. Primary malignant melanoma of cervix - a case report. *Indian J Cancer*. 2005;42(4):201–204. doi:10.4103/0019-509X.19206
13. Cid JM. [Melanoid pigmentation of the endocervix. A neurogenistic visceral argument]. *Bol Soc Cir Rosario*. 1959;24:63–78.
14. Goldman RL, Friedman NB. Blue nevus of the uterine cervix. *Cancer*. 1967;20(2):210–214. doi:10.1002/1097-0142(1967)20:2<210::AID-CNCR2820200206>3.0.CO;2-S
15. Szumiło J, Patel A, Patel S, Burdan F. Blue nevus of the endocervix. *Folia Morphol*. 2010;69(1):62–64.
16. Feichter G, Curschellas E, Gobat S, et al. Malignant melanoma of the uterine cervix; case report including cytology, histology and immunocytochemistry. *Cytopathology*. 1995;6(3):196–200.
17. Zamiati S, Sahraoui S, Jabri L, et al. [Primary malignant melanoma of the cervix uteri: apropos of 1 case with review of the literature]. *Gynecol Obstet Fertil*. 2001;29(5):381–385. doi:10.1016/S1297-9589(01)00148-5
18. Hasan S, Jamdar S, Jangra J, et al. Oral malignant melanoma: an aggressive clinical entity - report of a rare case with review of literature. *J Int Soc Prev Community Dent*. 2016;6(2):176–181. doi:10.4103/2231-0762.175145
19. McLaughlin CC, Wu X-C, Jemal A, et al. Incidence of noncutaneous melanomas in the U.S. *Cancer*. 2005;103(5):1000–1007. doi:10.1002/cncr.20866
20. Rünger TM, Klein CE, Becker JC, et al. The role of genetic instability, adhesion, cell motility, and immune escape mechanisms in melanoma progression. *Curr Opin Oncol*. 1994;6(2):188–196. doi:10.1097/00001622-199403000-00012
21. Khoo US, Collins RJ, Ngan HY. Malignant melanoma of the female genital tract. A report of nine cases in the Chinese of Hong Kong. *Pathology*. 1991;23(4):312–317. doi:10.3109/00313029109063595
22. Tomicic J, Wanebo HJ. Mucosal melanomas. *Surg Clin North Am*. 2003;83(2):237–252. doi:10.1016/S0039-6109(02)00100-7
23. Rohwedder A, Philips B, Malfetano J, et al. Vulvar malignant melanoma associated with human papillomavirus DNA: report of two cases and review of literature. *Am J Dermatopathol*. 2002;24(3):230–240. doi:10.1097/00000372-200206000-00008
24. Benson RJ, Tan LT. Radiation-induced malignant melanoma of the cervix. *Clin Oncol*. 2000;12(4):234–237.
25. Nai GA, Bazan A, Rocha CA, et al. Postpartum genital melanoma—a case report. *Rev Bras Ginecol Obstet*. 2018;40(3):163–167. doi:10.1055/s-0038-1624578
26. Udager AM, Frisch NK, Hong LJ, et al. Gynecologic melanomas: a clinicopathologic and molecular analysis. *Gynecol Oncol*. 2017;147(2):351–357. doi:10.1016/j.ygyno.2017.08.023
27. Ambrose M, Gatti RA. Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions. *Blood*. 2013;121(20):4036–4045. doi:10.1182/blood-2012-09-456897

28. Dalmasso B, Pastorino L, Nathan V, et al. Germline ATM variants predispose to melanoma: a joint analysis across the GenoMEL and MelaNostrum consortia. *Genet Med*. 2021;23(11):2087–2095. doi:10.1038/s41436-021-01240-8
29. Puri S, Yoonessi M, Romney SL. Malignant melanoma of the cervix uteri. *Obstet Gynecol*. 1976;47(4):459–462.
30. Pinedo F, Ingelmo JM, Miranda P, et al. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *Gynecol Obstet Invest*. 1991;31(2):121–124. doi:10.1159/000293117
31. Deshpande AH, Munshi MM. Primary malignant melanoma of the uterine cervix: report of a case diagnosed by cervical scrape cytology and review of the literature. *Diagn Cytopathol*. 2001;25(2):108–111. doi:10.1002/dc.2014
32. Pusceddu S, Bajetta E, Buzzoni R, et al. Primary uterine cervix melanoma resembling malignant peripheral nerve sheath tumor: a case report. *Int J Gynecol Pathol*. 2008;27(4):596–600. doi:10.1097/PGP.0b013e31817323c4
33. Mousavi AS, Fakor F, Nazari Z, et al. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *J Low Genit Tract Dis*. 2006;10(4):258–263. doi:10.1097/01.lgt.0000229564.11741.4e
34. Furuya M, Shimizu M, Nishihara H, et al. Clear cell variant of malignant melanoma of the uterine cervix: a case report and review of the literature. *Gynecol Oncol*. 2001;80(3):409–412. doi:10.1006/gyno.2000.6091
35. Amenssag L, El Idrissi F, Erchidi I, et al. [Primary malignant melanoma of the cervix]. *Presse Med*. 2002;31(21 Pt 1):976–978.
36. Bishop PW, Menasce LP, Yates AJ, et al. An immunophenotypic survey of malignant melanomas. *Histopathology*. 1993;23(2):159–166. doi:10.1111/j.1365-2559.1993.tb00474.x
37. Argenyi ZB, Cain C, Bromley C, et al. S-100 protein-negative malignant melanoma: fact or fiction? A light-microscopic and immunohistochemical study. *Am J Dermatopathol*. 1994;16(3):233–240. doi:10.1097/00000372-199406000-00002
38. Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. *Histopathology*. 2000;36(5):387–402. doi:10.1046/j.1365-2559.2000.00894.x
39. Uzüm N, Köse F, Ataoğlu O. Metastatic malignant melanoma of the uterine cervix: first diagnosed on liquid-based cytology. *Diagn Cytopathol*. 2008;36(11):769–772. doi:10.1002/dc.20917
40. Gupta S, Sodhani P, Jain S. Primary malignant melanoma of uterine cervix: a rare entity diagnosed on fine needle aspiration cytology--report of a case. *Cytopathology*. 2003;14(3):153–156. doi:10.1046/j.1365-2303.2003.00014.x
41. Sugiyama VE, Chan JK, Kapp DS. Management of melanomas of the female genital tract. *Curr Opin Oncol*. 2008;20(5):565–569. doi:10.1097/CCO.0b013e32830b0dda
42. Norris HJ, Taylor HB. Melanomas of the vagina. *Am J Clin Pathol*. 1966;46(4):420–426. doi:10.1093/ajcp/46.4.420
43. Wydra D, Sawicki S, Ciach K, et al. Malignant melanoma of the uterine cervix. *Eur J Obstet Gynecol Reprod Biol*. 2006;124(2):257–258. doi:10.1016/j.ejogrb.2005.06.024
44. Salle E, Houvenaeghel G, Bladou F, et al. [Malignant melanoma of the uterine cervix. Apropos of a case, with total colpo-hysterectomy and vaginal reconstruction using a rectus abdominis flap]. *Ann Chir*. 1998;52(1):93–96.
45. Noguchi T, Ota N, Mabuchi Y, et al. A case of malignant melanoma of the uterine cervix with disseminated metastases throughout the vaginal wall. *Case Rep Obstet Gynecol*. 2017;2017:5656340. doi:10.1155/2017/5656340
46. Association, C.C.C.o.C.A.-C.. 原发性子宫颈恶性黑色素瘤诊断及治疗指南(2024)年版. 中国实用妇科与产科杂志. 2024;40(2):166–172.
47. Santoso JT, Kucera PR, Ray J. Primary malignant melanoma of the uterine cervix: two case reports and a century's review. *Obstet Gynecol Surv*. 1990;45(11):733–740. doi:10.1097/00006254-199011000-00003
48. Jones HW, Droegemueller W, Makowski EL. A primary melanocarcinoma of the cervix. *Am J Obstet Gynecol*. 1971;111(7):959–963. doi:10.1016/0002-9378(71)90953-7
49. Genton CY, Kunz J, Schreiner WE. Primary malignant melanoma of the vagina and cervix uteri. Report of a case with ultrastructural study. *Virchows Arch a Pathol Anat Histol*. 1981;393(2):245–250. doi:10.1007/BF00431080
50. Cantuaria G, Angioli R, Nahmias J, Estape R, Penalver M. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *Gynecol Oncol*. 1999;75(1):170–174. doi:10.1006/gyno.1999.5491
51. Cantuaria G, Angioli R, Fernandez-Abril A, et al. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *Prim Care Update Ob Gyns*. 1998;5(4):159–160. doi:10.1016/S1068-607X(98)00052-3
52. Kristiansen SB, Anderson R, Cohen DM. Primary malignant melanoma of the cervix and review of the literature. *Gynecol Oncol*. 1992;47(3):398–403. doi:10.1016/0090-8258(92)90148-C
53. Ye Y, Fu A, Cai J, et al. Primary malignant melanoma of the cervix: a comprehensive analysis of case reports in the Chinese population. *Cancer Med*. 2023;12(13):14052–14061. doi:10.1002/cam4.6054
54. Bajetta E, Del Vecchio M, Nova P, et al. Multicenter Phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. *Ann Oncol*. 2006;17(4):571–577. doi:10.1093/annonc/mdl007
55. Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist*. 2011;16(1):5–24. doi:10.1634/theoncologist.2010-0190
56. Myriokefalitaki E, Babbel B, Smith M, et al. Primary malignant melanoma of uterine cervix FIGO IIa1: a case report with 40 months ongoing survival and literature review. *Gynecol Oncol Case Rep*. 2013;5:52–54. doi:10.1016/j.gynor.2013.04.004
57. Vleugels MP, Brölmann HA, van Beek M. Primary melanoma of the cervix uteri, an avis rara? A review of the literature. *Acta Obstet Gynecol Scand*. 1990;69(3):259–264. doi:10.3109/00016349009028690
58. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–723. doi:10.1056/NEJMoa1003466
59. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517–2526. doi:10.1056/NEJMoa1104621
60. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. *J Clin Oncol*. 2011;29(21):2904–2909. doi:10.1200/JCO.2010.33.9275
61. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107–114. doi:10.1056/NEJMoa1203421

62. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a Phase 1 trial. *Lancet*. 2014;384(9948):1109–1117. doi:10.1016/S0140-6736(14)60958-2
63. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, Phase 2 trial. *Lancet Oncol*. 2015;16(8):908–918. doi:10.1016/S1470-2045(15)00083-2
64. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521–2532. doi:10.1056/NEJMoa1503093
65. Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA*. 2016;315(15):1600–1609. doi:10.1001/jama.2016.4059
66. Suzuki R, Endo H, Sasaki T, et al. Primary malignant melanoma of uterine cervix treated with pembrolizumab as adjuvant immunotherapy. *Int Cancer Conf J*. 2021;10(3):254–258. doi:10.1007/s13691-021-00477-z
67. Colombino M, Capone M, Lissia A, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. *J Clin Oncol*. 2012;30(20):2522–2529. doi:10.1200/JCO.2011.41.2452
68. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507–2516. doi:10.1056/NEJMoa1103782
69. Hauschild A, Grob -J-J, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, Phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–365. doi:10.1016/S0140-6736(12)60868-X