

Metastatic malignant melanoma of the uterus diagnosed by colposcopy

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SUMMARY

Introduction Primary and metastatic malignant melanomas represent a rare diagnosis with a small number of described cases. The aggressive nature of the tumor, non-specific symptoms, difficult diagnosis, and no official protocol about the treatment result in poor disease prognosis.

Case Outline The authors presented a 41-year-old multigravida patient. She had an operation of malignant melanoma in the occipital area of the head. She went to her gynecologist because of increased pale pink vaginal secretion. Gynecological examination didn't show any significant abnormalities apart from a slightly enlarged uterus. Papanicolaou test and vaginal secretion examination were normal. Colposcopically, a significant dark brown hyperpigmented area around 1 cm in size was observed on the posterior lip of the cervix, near the orifice and cervical canal, suspicious of melanoma, which was proven on targeted biopsy of the hyperpigmented change on the cervix, and by magnetic resonance imaging of the lesser pelvis. Classic hysterectomy with adnexectomy and regional pelvic lymphadenectomy were performed.

Conclusion This case report pointed out the significance of applying colposcopy in diagnosing suspected metastatic melanoma of the uterine cervix, along with other diagnostic methods and anamnestic data.

Keywords: malignant melanoma; uterus; colposcopy; metastases

INTRODUCTION

Malignant melanoma (MM) of the skin is a tumor developed by malignant transformation of melanocytes. The term comes from the pigment melanin, which is most frequently present although its forms are clinically different, from hyperpigmented to amyloid [1]. A common characteristic of all MMs is that they are locally aggressive and prone to early lymphogenic and vascular metastases [2]. The percentage of MMs in relation to all carcinomas is 1%, and estimated incidence of MMs in the genital region is in 3–7% range, out of which the vulva is the most common site of melanoma occurrence [3]. Due to such a low incidence, MM of the uterine cervix is a rare entity. Since 1989, only about 81 cases of uterine MMs have been described in the literature [4].

With respect to gender, the frequency of MM in the incidence of all malignant tumors is 1.6% for men and 1.5% for women [5].

CASE REPORT

The patient was a 41-year-old multigravida female. She went to her gynecologist in November 2014 because of increased pale pink vaginal secretion. Anamnesis showed that the patient had no previous serious gynecological problems and that she had been regularly undergoing routine gynecological examinations. Her medi-

cal history showed that one year previously she underwent an excision of hyperpigmented skin change in the occipital area of the head. The operation was performed in October 2013. Histopathology after the surgical excision of the lesion showed melanoma malignum nodular cutis exulcerans. The cells were epithelioid and a significant inflammatory infiltration (peritumoral and tumoral) was present, necrotic and ulcerative areas were observed, there was no angioinvasion and the number of mitoses was 10/mm². The skin lesion was completely removed (including more than 2 cm of the surrounding healthy tissue). The disease was graded level III according to Breslow (10 mm) and level IV according to Clark. Considering that the lesion was removed along with a region of healthy tissue and that X-ray of the lungs and echo of the liver and soft tissue were normal, the consulting doctors decided that there were no indications for specific oncologic treatment and suggested future monitoring with new analyses and tests to be performed in two months.

Until her visit to the gynecologist, there was no evidence of recurrence of the primary disease.

The patient did not see her gynecologist in the previous year. The last Papanicolaou test and colposcopy were performed when primary MM was diagnosed and surgically removed, and the findings were normal.

General examination of the visible skin did not show any new pigmented skin lesions. Gy-

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necological examination did not show any significant abnormalities. The vulva and vagina were normal with no macroscopically visible changes on the cervix, except for slight pinkish secretion flowing from external orifice of the cervical canal to posterior vaginal fornix. The uterus in anteversoflexion was slightly enlarged, which corresponds to the size of uterus after two deliveries (as is the case with our patient). Adnexa could not be palpated. Parametrium was without changes. During the examination, smears were taken for Papanicolaou test and vaginal secretion was sampled.

Papanicolaou test results were normal (PA: NILM). Vaginal secretion examination was also normal (group II). The patient was referred to the Clinic of Gynecology and Obstetrics, where colposcopy and pelvic ultrasound were performed.

Colposcopy findings were satisfactory. Transition zone was completely visualized (TYPE 1). Exocervical epithelium was squamous and iodine positive. A significant dark brown suspected hyperpigmented area around 1 cm in size was observed at 9 o'clock position, near the orifice and cervical canal. Figure 1 shows the cervix after it was covered with acetic acid. The epithelium of the exocervix is squamous, its pale pink color is normal, and it is covered with irregular, spotty area of dark brown pigmentation at 9 o'clock position. Figure 2 shows the colposcopic image of the same cervix after it was covered with Lugol's solution. It can be observed that there is the area of re-epithelialization around the orifice, partially iodine positive, and part of the cervix around the orifice at 9 o'clock position where previously hyperpigmentation was located, which appeared gray-blue after reacting to Lugol's solution.

The ultrasound examination showed the uterus in anteversoflexion (normal anatomical position), 9 cm in size, with endometrium which was hyperechogenic along the cavum and extended into the cervical canal 25 mm wide in the widest part of the central areas. The adnexa had normal position and size. The pouch of Douglas was empty and without free fluid.

Targeted biopsy of the hyperpigmented change on the cervix was performed, as well as fractional explorative curettage of the cervical canal and uterine cavity.

Histopathology findings of cervix biopsy and cervical canal and cavity curettage also showed malignant melanoma.

In order to check for local spread of the disease and possible presence of other metastases, the patient underwent magnetic resonance imaging of the lesser pelvis, X-ray of the lung, and echo of the liver. Magnetic resonance imaging findings confirmed the presence of tumors in the uterine cavity and cervix, which could correspond to secondary MM deposits, as shown in Figures 3 and 4. The change was described as heterogeneous (predominantly hyper-, but also hypodense), partially entering the stroma but without penetrating the myometrium or spreading to parametrium. The X-ray of the lungs, echo of the liver, and examination of other systems did not point to the presence of other suspicious metastatic deposits.

The patient and all her medical records were presented to consulting oncologists. Considering the localized solitary metastatic process, the consulting doctors decided to per-



Figure 1. Colposcopic image of malignant melanoma after coating the cervix with acetic acid

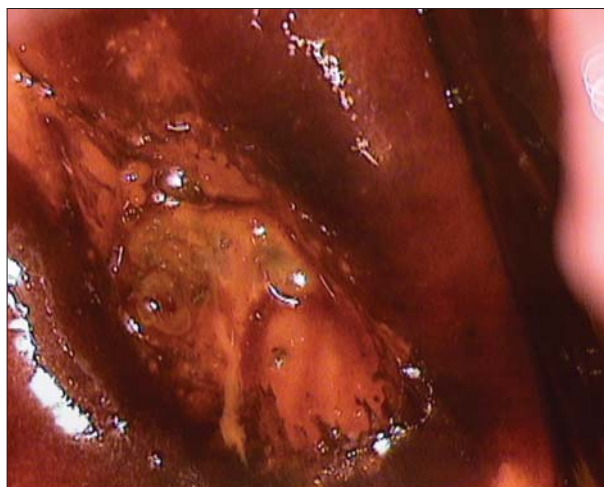


Figure 2. Malignant melanoma of the cervix after coating with Lugol's solution

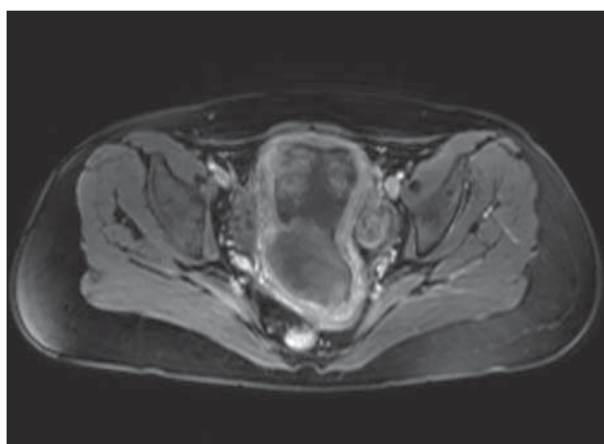


Figure 3. Magnetic resonance imaging of the lesser pelvis – cross section

form classic hysterectomy with adnexectomy and regional pelvic lymphadenectomy. After the surgery, the patient's histopathology findings were to be examined again by the consulting doctors in order to decide on further treatment.

The surgery was performed on December 19, 2014. The surgery was uneventful. Apart from slightly enlarged and

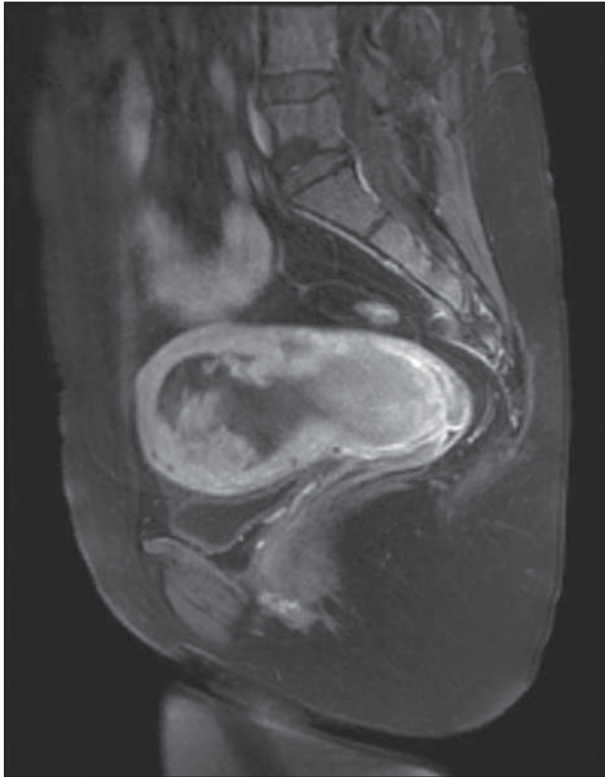


Figure 4. Magnetic resonance imaging of the lesser pelvis – longitudinal section

softened uterus, intraoperative findings of the lesser pelvis did not show any other changes. Palpation and exploration of other organs of the abdominal cavity (intestines, omentum, liver, peritoneum) did not reveal any pathological changes and hyperpigmentation. Figure 5 shows the longitudinal and cross-sectional sample of the surgically removed uterus.

The final postoperative histopathological findings showed presence of malignant melanoma in the tissue of the cervix and corpus with areas of cells of epithelioid and fusiform type, dark granulated pigmentations with number of mitoses around 8 mm². The sampled fat tissue and regional iliac lymphatic nodes did not have any metastatic processes.

Immunohistochemical staining confirmed the diagnosis of MM in uterus, as shown in Figures 6 and 7. Tissue samples were fixed in 10% buffered formalin solution, embedded in paraffin wax, divided into 4 µm thick sections and stained with hematoxylin and eosin. Representative material was stained with a panel of antibodies using the labeled streptavidin-biotin-peroxidase complex method according to the manufacturer's instructions (LSAB Kit, Dako, Glostrup, Denmark). The primary antibodies used were mouse monoclonal antibodies for melanosome (clone HMB-45) and rabbit polyclonal antibody for S-100 protein. The chromogen was 3, 3'-diaminobenzidine (DAB), and the slides were lightly counterstained with Meyer's hematoxylin. All reagents were acquired from Dako company.

According to anamnestic data, immunohistochemical parameters and the absence of junctional changes, the malignant melanoma of the uterus was considered to be a metastatic process.



Figure 5. Longitudinal and cross-sectional macroscopic appearance of the surgically removed uterus

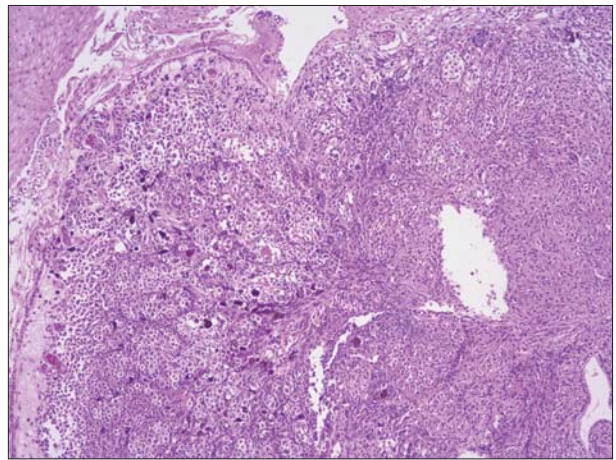


Figure 6. Atypical epithelioid melanocytes with pleomorphic nuclei and abundant cytoplasm with dusty melanin (H&E, ×10)

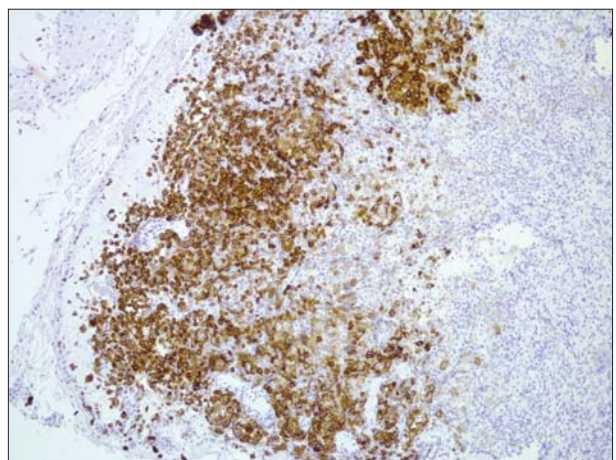


Figure 7. Diffuse immunoreactivity of HMB-45 (Streptavidin-biotin-peroxidase complex method, Meyer's hematoxylin counterstain, ×10)

Postoperative course was uneventful. The patient was generally well, released from gynecology clinic and advised to refer to the consulting oncologists for mixed-type localization (which deals with treatment and monitoring of MM) for further monitoring and continuation of specific oncological treatment of MM.

The consulting panel of doctors referred the patient to positron emission tomography to evaluate the disease spread. The patient has not returned for further check-ups since.

DISCUSSION

The degree of MM invasion can be determined in two ways: measuring the thickness of the infiltrated skin (according to Clark) and measuring the thickness of tumor in millimeters (according to Breslow) [6, 7].

Survival depends on the stage of the disease as well as its location. The prognosis and survival are most favorable when MM is located in the extremities, then the trunk, and the worst prognosis is obtained when MM is in the area of the head and neck [8].

About 20% of patients with skin MM have recurrent disease. The most common location is the place of previous treatment and regional lymphatic glands. Distant visceral metastases are most often found in the lungs, the liver and the brain. With regard to time, metastases are most frequently detected within the first five years after diagnosis [9].

In patients with metastatic disseminated changes, the prognosis is poor and characteristics and classification of the primary tumor (according to both Clark and Breslow) are no longer significant for prognosis and outcome. The treatment in these cases is palliative and its goal is to reduce the tumor mass and prevent complications caused by metastases [10].

The most important prognostic parameters for patients with distant metastatic changes are the number of metastatic places, their location, and length of remission [11].

Patients with one metastatic location have higher survival probability than patients with numerous metastases [12]. Patients with skin metastases have better prognosis than those with visceral metastases [11]. Distant metastases in lymphatic nodes and soft tissues are present in 59% of cases, while visceral metastases are most common in the lungs, with 31–36% of cases [13]. The prognosis depends on the number of lymphatic nodes with metastases, not on their size. The location of metastatic lymphatic nodes is also important because it has been demonstrated that patients with infiltrated armpit lymphatic nodes more often develop visceral metastases than patients with infiltrated inguinal nodes [14].

The concept of primary MM of the cervix is a rare diagnosis, which originated in 1960, when Cid [15] described melanocytic cells in the cervix.

This is an aggressive malignant tumor with late diagnosis because it causes non-specific problems that do not point to this disease. Apart from sparse non-specific symptoms which most often include increased vaginal secretion or irregular bleeding, there are no other specific symptoms. It can clinically manifest itself in the form of exophytic proliferation or polyps of red, blue, dark or dark brown color [16].

Cytological and histopathological picture is also not specific, especially with non-pigmented tumor cells. Pathological preparation shows strings of pleomorphic anaplastic cells with large, round or oval nucleus with protruded nucleolus and sparse cytoplasm in which yellow-brown melanin-positive pigment can be observed [17].

Cytological smear of uterine cervix MM can be normal and false-negative [18].

As an additional support to histological and differential diagnosis, immunohistochemical staining is used, including monoclonal bodies to melanin, anti-S-100 protein, anti-tyrosinase, anti-Mart-1/Melan-A and HMB-4 [19].

A particular problem appears with differential diagnosis of primary and metastatic MM of the cervix. The criteria proposed by Norris and Taylor [20] can help to differentiate primary from secondary MM of the cervix. According to these criteria, primary MMs are characterized by the following: 1) presence of melanin in the cervical epithelium; 2) absence of melanoma in other parts of the body [20, 21], and 3) evidence of junctional changes in the cervix.

The treatment of MM is primarily surgical and in some cases it can include chemotherapy, radiological, and immunological treatment [22]. Surgical treatment of cervical MM implies radical hysterectomy with or without lymphadenectomy, with upper vaginectomy [23]. Radiation therapy in MM has shown limited indications due to the relative radioresistance and is usually reserved as a treatment for palliation of recurrent disease, advanced disease, involved surgical margins, and involved lymph nodes [16]. Immunotherapy means application of high-dose interleukin-2 and is given to a small number of patients with metastatic disease [24]. As for chemotherapy, the most commonly used combination has been cisplatin, bleomycin, and vinblastine, or dacarbazine monotherapy in advanced stages of the disease [25].

Staging of uterine cervix MM is performed by the International Federation of Gynecology and Obstetrics (FIGO) staging, but very often American Joint Committee on Cancer (AJCC) staging is used for indicating the extent of the disease, stages of the disease, involvement of lymph nodes and distant metastases [26].

However, due to a small number of described cases, there are no sufficient statistical data or official recommendations in terms of therapeutic protocol and monitoring of MM located in the uterus. Literature mostly describes the initial treatment which consists of radical hysterectomy, which may or may not be associated with lymphadenectomy. Therefore, having all the described facts in mind, the prognosis is poor and includes early visceral metastases [16].

Primary and metastatic MMs represent a rare diagnosis with a small number of described cases. The aggressive nature of the tumor, non-specific symptoms, difficult diagnosis and no official protocol on the treatment result in poor disease prognosis. This paper points out the significance of colposcopy in identifying and diagnosing malignant melanoma of the uterine cervix in patients who had undergone melanoma surgery.

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Метастатски малигни меланом материце дијагностикован колпоскопијом

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КРАТАК САДРЖАЈ

Увод Примарни и метастатски малигни меланоми представљају ретку дијагнозу са малим бројем описаних случајева. Агресивна природа тумора, неспецифични симптоми, тешка дијагноза и неофицијални терапијски протокол резултују у лошој прогнози болести.

Приказ болесника Аутори су представили 41 годину стару вишеротку као пацијенткињу. Она је имала операцију малигног меланом окципиталне регије поглавине. Отишла је код свог гинеколога због бледе ружичасте вагиналне секреције. Гинеколошки преглед сем лако увећане материце није показао никакве сигнификатне абнормалности. ПАП тест и преглед вагиналног секрета су били нормални. Колпоскопски – присутно је сигнификантно тамно браон

хиперпигментовано поље око 1 cm у промеру, опсервирано на задњој усни грлића материце, поред орифицијума и цервикалног канала, које је било суспектно на меланом, што је доказано циљаном биопсијом хиперпигментисане промене цервикса и магнетном резонанцом мале карлице. Урађена је класична хистеректомија са аднексектомијом и регионалном пелвичном лимфаденектомијом.

Закључак Овај приказ случаја је показао могућност колпоскопије да укаже на суспектан налаз на грлићу материце, који у склопу осталих дијагностичких и анамнестичких параметара може да помогне у дијагнози метастатског меланом материце.

Кључне речи: малигни меланом; материца; колпоскопија; метастазе