INTRODUCTION

Cervical cancer is the most common cancer in women from developing countries. 90% of the cervical cancer are squamous cell carcinoma, 2-4% are adenocarcinoma and the rest other histological types, like adenosquamous carcinoma, small cell carcinoma, clear cell carcinoma, lymphoma or sarcoma. Malignant melanoma in the female genital tract accounts for 3% to 7% of this type of tumors, with the majority occurring in the vulva and vagina. Due to such a low incidence, malignant melanoma of the
uterine cervix is a rare histologic entity, with few reports of primary malignant melanoma of the cervix currently available in the literature. The late diagnosis, in advanced stage, local aggressiveness and early lymphogenic and vascular metastases generate a very poor overall prognosis. A recent National Cancer Database report indicates a 5-year survival of 11.4% for female genital tract melanoma.

Malignant melanoma is a common neoplasm of the skin and mucous membranes (oral cavity, esophagus, conjunctiva, anus, gynecological tract) accounting for 1.6% of all cancer cases. It is a tumor developed from malignant transformation of melanocytes, in close relationship to sun exposure. The term comes from malignant transformation of melanocytes, in the uterine cervix: 1) melanocytes migrate from neural crest to the uterine cervix; 2) melanocytes differentiate from the endocervical epithelium; 3) melanocytic cells originate from Schwannian cells. The most accepted theory is the first one, the embryologic migration of melanocytes from the neural crest.

Etiopathogenesis of cervical uterine malignant melanoma is not well defined, but genetic predisposition along with microenvironmental, hormonal and infectious factors are incriminated. Rohwedder et al. recently pointed out the relation between human papillomavirus (HPV) infection and primary gynecological malignant melanoma. The authors report the presence of HPV subtype 16 in two cases of vulvar malignant melanoma.

Pathologic and clinical features

Diagnosis of cervical malignant melanoma is usually established by gynecological examination associated with histopathological and immunohistochemical evaluation.

Malignant melanoma of the cervix is more frequent in postmenopausal women, with a median age of 59 years (range 20-78 years). Non-specific symptomatology delays the diagnosis. Vaginal bleeding (63.6%), vaginal mass (15.9%), and vaginal discharge (15.9%) are common symptoms of female genital tract malignant melanoma, along with abdominal pain, dyspareunia, and postcoital bleeding. In addition, as it occurs in invisible locations, symptoms may be unnoticed until the tumor has reached a certain size.

The gross findings of genital malignant melanoma include various shapes of lesions, from solitary, multifocal, superficial spreading to exophytic proliferation/polyps of red, blue, dark or dark brown color. 6% of cases are amelanotic lesions and this absence of melanin pigment can lead to misdiagnosis as carcinomas, sarcomas or other forms of malignancy. Exclusion of any other primary sites of melanoma and immunohistochemical evaluation using monoclonal bodies to melanin, anti-S-100 protein, anti-tyrosinase, anti-Mart-1/Melan-A and HMB-45 confirms the diagnosis.

Imaging studies (CT, MRI, PET/CT) are useful in the evaluation of the extension of the tumor, lymph node or distant metastases and in the identification of the primary site of malignancy. Metastasis to the lower female genital tract is rare, mainly from adjacent organs as bladder and colorectum and rarely from kidney or breast. MRI is especially useful in melanoma evaluation as it has a distinct signal pattern for melanin, high signal intensity on T1-weighted magnetic resonance images and low signal intensity on T2-weighted magnetic resonance images.
superior to MRI and CT for sensitivity, specificity and accuracy in detecting pelvic nodal metastasis.

The role of PET-CT for staging cutaneous malignant melanoma has been reported to have high sensitivity and accuracy, but there are no significant reports on the role of PET or PET/CT in the clinical management of malignant melanomas arising from female reproductive organs.

Survival of the patients with malignant melanoma depends on the stage of the disease and its location. The prognosis and survival are most favorable when malignant melanoma is located in the extremities, than the trunk. The area of the head and neck has the worst prognosis. The degree of malignant melanoma 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).

In uterine cervix malignant melanoma, the extent of the disease, lymph nodes involvement and distant metastases can be evaluated according to the International Federation of Gynecology and Obstetrics (FIGO) staging or American Joint Committee on Cancer (AJCC) staging. Morrow and Di Saia suggested that the primary cutaneous melanoma staging system based on the thickness of the primary lesion is more clinically applicable compared to FIGO staging. When examining differences in survival distribution for Breslow thickness, lymph node status, systemic therapy, and surgery, Tcheung et al. found that only increasing Breslow depth was associated with decreased survival. However, some authors prefer the FIGO staging system than the Clark and Breslow scales, because the FIGO staging system correlates better with prognosis. Survival is inversely correlated with both Breslow tumor thickness and increasing FIGO stage.

Similarly, for primary malignant melanoma of the vagina a few recent studies reported that the AJCC staging system based on the guidelines for cutaneous malignant melanoma reflects better the overall prognosis for vaginal melanoma than the FIGO staging. In these studies, invasion depth, margin, and lymph node status were found major prognostic factors.

**TREATMENT**

Because of the rarity of primary cervical melanoma and the small number of cases in the literature, there are no prospective, randomized, clinical trials assessing the effectiveness of various treatment options.

The basis of treatment is surgical excision with the aim at achieving local control. In a study of patients with vaginal malignant melanoma at the University of Texas MD Anderson Cancer Center, the median survival was significantly different for women with vaginal malignant melanoma who underwent surgery, compared to those who received other therapeutic modalities without surgery. There is a debate regarding the extent of the surgery: wide local excision versus radical surgery. Radical surgery implies a radical hysterectomy with or without pelvic lymphadenectomy and/or superior vaginectomy. Some authors consider it the best approach since the first operation is the optimal chance for treatment, as surgery for recurrent disease has less favourable results.

The opponents of radical approach reported that aggressive local excision with adequate surgical margins, of at least 2 cm, results in similar survival rates as radical surgery. However, as tumor thickness increases, safe surgical excision margin width should also be increased. The beneficial role of routine lymphadenectomy is another debated issue. It should be performed in cases with large tumors and in the presence of pigmented lymph nodes, which signifies a high risk of lymph node involvement. However, the 5-year survival rate is less than 20% in patients with macroscopically involved lymph nodes. In order to decrease the rate of morbidity, sentinel lymph node biopsy is gaining popularity, but there are not sufficient statistically significant data so far.

There is limited evidence about the optimal adjuvant therapy for malignant melanoma of the cervix. Although malignant melanoma is known to be resistant to radiotherapy and chemotherapy, recent studies showed that adjuvant treatment (including radiotherapy and chemotherapy) prolonged progression-free survival in vaginal malignant melanoma patients who underwent wide local excision. In malignant melanoma of the cervix, radiotherapy is reserved for advanced disease, inadequate surgical margins, parametrial invasion, residual tumors or pelvic lymph node involvement or as palliative treatment in recurrences. Postoperative chemotherapy is a viable treatment option in advanced, recurrent or metastatic cervical malignant melanoma. The same protocols used for skin melanoma are applied, using cisplatin, bleomycin, vinblastine or dacarbazine, with an objective response (transient regression of tumors), but without a significantly improved survival.

**Immunotherapy** including the BCG (Bacille Calmette-Guérin) with interferon or interleukin-2 is a part of the therapeutic arsenal. Two agents (ipilimumab – the anti-CTLA-4 antibody and vemurafenib – the BRAF kinase inhibitor) were approved by the US Food and Drug Administration in 2011 for the treatment of unresectable or metastatic cutaneous melanoma and they show promising results in the treatment of genital tract malignant melanoma.
Bathia et al. showed promising results in cases with metastatic disease when using immunotherapy with high dose interleukin-2.

Due to the above debated issues and the limited data, each patient’s treatment should be individualized.

Malignant melanoma of the uterine cervix is highly aggressive tumor as both local recurrence and distant metastases usually occur within a few months to several years from initial diagnosis. Studies on other malignant melanoma, like anorectal, where larger number of cases exists, have shown that resection status and tumor stage are independent prognostic variables and provided clear resection margins, there is a significantly better overall 5-year survival.

Recurrence in malignant melanoma of the cervix develops in 20% of the patients and is more commonly local (vagina, vulva or alongside suture line) or in regional lymph nodes. Distant metastases involve the lymph nodes and soft tissue in up to 59% of cases, while visceral metastases are most common in the lungs (31-36% of cases), followed by the liver and the brain. In patients with metastatic disease, the prognosis is poor and classification of the primary tumor (according to Clark and Breslow) is no longer significant for the outcome. The most important prognostic parameters for patients with distant metastatic changes are the number of metastatic places and their location. Patients with one metastatic location or skin metastases have better prognosis than those with numerous metastases or visceral metastases. The prognosis depends also on the number of positive lymph nodes and the location of metastatic lymph nodes. It has been demonstrated that patients with infiltrated armpit lymphatic nodes more often develop visceral metastases than patients with infiltrated inguinal nodes. In metastatic disease, the treatment is palliative with the aim of reducing the tumoral mass and preventing complications induced by metastases.

However, regardless of stage and treatment, the overall prognosis of primary cervical malignant melanoma is very poor, as it is usually diagnosed at an advanced stage and it disseminates by hematogenic route at early stages. Survival range between 0.1 month and 14 years. Studies have indicated that 87.5% patients die due the disease in the first three years after the initial diagnosis (22.9 months overall survival). The 5-year survival is 18.8% for stage I, 11.1% for stage II and 0% for stages III-IV.

Conclusions

Primary cervical malignant melanomas are very rare tumors, that should be considered in the differential diagnosis of poorly differentiated malignant neoplasms involving the uterine cervix. It is very important to rule out metastasis from common primary sites such as skin, oesophagus, uveal tract and anorectal region before considering diagnosis of primary cervical melanoma. The pathological diagnosis is usually confirmed by immunohistochemistry and the surgical resection continues to form the basis of primary treatment. The aggressive nature of the tumor, non-specific symptoms, late diagnosis and no official therapeutic protocol result in very poor disease prognosis.

References

2. Xia L, Han D, Yang W, Li J, Chuang L, Wu X. Primary malignant melanoma of the vagina: a retrospective clinicopathologic study of 44 cases. Int J Gynecol Cancer 2014;24:149-55
18. Deniz Ark, Tufan Oge, Sare Kabukcuoglu, Omer Tarik Yalcin, Sinan Ozalp. Anmelanotic Malignant Melanoma of the Uterine Cervix Diagnosed by Cervical smear. Diagnostic Cytopathology 2016;44(6)
34. E. Myriokefalitaki, B. Babbel, M. Smith, A.S. Ahmed. Primary malignant melanoma of uterine cervix FIGO Iia1:A case report with 40 months ongoing survival and literature review. Gyn Oncol Reports 2013;5;52-54
36. Yaj-Lu Tsai, Pei-Wei Shuang, Sheng-Chien Chan, Wen-Yu Chuang, Yu-Chien Shia, Chung-Huei Hsu. Uterine cervical melanoma presenting with rapid progression detected by PET/CT. Acta Radiologica Short Reports 2012; 1