Case report

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Primary vaginal melanoma

Irena Conić[1,2], Slavica Stojnev[3,4], Ivan Petković[1,2], Dane Krtinić[2,5], Marijana Milović-Kovačević[6,7]

[1]University of Niš, Faculty of Medicine, Department of Oncology, Niš, Serbia
[2]University Clinical Center Niš, Clinic for Oncology, Niš, Serbia
[3]University of Niš, Faculty of Medicine, Department of Pathology, Niš, Serbia
[4]University Clinical Center Niš, Center for Pathology, Nis, Serbia
[5]University of Niš, Faculty of Medicine, Department for Pharmacology with Toxicology, Niš, Serbia
[6]University of Belgrade, Faculty of Medicine, Department of Oncology, Belgrade, Serbia
[7]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Contact: Irena Conić
81. dr Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: irena.conic@medfak.ni.ac.rs

Primary vaginal melanoma is a rare type of mucosal melanoma that constitutes 0,3% to 0,8% of all melanomas in women, and less than 3% of vaginal malignancies.

A 78-year-old female had complaints of a vaginal tingling, vaginal watery discharge, and dysuria for 4 months with a slowly increasing frequency over time. The patient underwent the complete tumor excision. Immunohistochemically, tumor cells were strongly positive for the SOX10, HMB-45, and S100 protein. The histopathological analysis of the whole tumor showed epithelioid melanoma cells in the vertical (invasive) growth phase with no evidence of the preceding radial growth. Most of the tumor cells contained a dark-brown intracellular pigment. Superficial microscopic ulceration was present. The Breslow tumor thickness was 12 mm. The

tumor-infiltrating lymphocytes (TILs) were non-brisk and the mitotic rate was 15 mitotic figures per 1mm2. Lymphovascular invasion was positive. Perineural and intraneural infiltration was not noticed. Tumor regression and the microscopic satellites were absent. The deep resection margin was free of the tumor cells. According to the AJCC8th stage grouping for melanoma, this case was of stage IIC (T4b, N0, M0).

Surgical resection with WLE remains the mainstay in the treatment of this aggressive disease with poor overall survival. Mucosal melanoma that arises in vaginal walls is often clinically indiscernible lesion, thus prompt biopsy, timely and accurate diagnosis is of crucial significance.

Keywords*:* vaginal melanoma, melanocytes, mucosal melanomas

Prikaz slučaja

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Primarni melanom vagine

Irena Conić[1,2], Slavica Stojnev[3,4], Ivan Petković[1,2], Dane Krtinić[2,5], Marijana Milović-Kovačević[6,7]

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra za onkologiju, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za onkologiju, Niš, Srbija
[3]Univerzitet u Nišu, Medicinski fakultet, Katedra za patologiju, Niš, Srbija
[4]Univerzitetski klinički centar Niš, Klinika za patologiju, Niš, Srbija
[5]Univerzitet u Nišu, Medicinski fakultet, Katedra za farmakologiju sa toksikologijom, Niš, Srbija
[6]Univerzitet u Beogradu, Medicinski fakultet, Katedra za onkologiju, Beograd, Srbija
[7]Institut za onkologiju i radiologiju Srbije, Beograd, Srbija

Contact: Irena Conić
81. dr Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: irena.conic@medfak.ni.ac.rs

Primarni melanoma vagine je redak tip melanoma sluzokože koji čini 0,3% do 0,8% svih melanoma kod žena, a manje od 3% maligniteta vagine.

Žena stara 78 godina žalila se na tegobe u vidu peckanja u vagini, vodenasti iscedak iz vagine i dizuriju poslednja 4 meseca sa povećanom učestalosti tokom vremena. Kod pacijentkinje je urađena potpuna ekscizija tumora. Imunohistohemijski, tumorske ćelije su bile snažno pozitivne na SOX10, HMB-45 i S100 protein. Histopatološka analiza tumora pokazala je ćelije epitelioidnog melanoma u vertikalnoj (invazivnoj) fazi rasta. Većina tumorskih ćelija je sadržala tamno-braon intracelularni pigment i prisustvo površinske mikroskopske ulceracije. Debljina tumora bila je 12 mm. Mitotička stopa je bila 15 mitotičkih figura po 1 mm2 sa limfovaskularnom invazijom koja je bila pozitivna. Perineuralna i intraneuralna infiltracija nije primećena. Regresija tumora i

mikroskopski sateliti su bili odsutni. Na margini duboke resekcije nije bilo tumorskih ćelija. Prema grupi AJCC8. stadijuma za melanom, ovaj slučaj je bio stadijuma IIC (T4b, N0, M0).

Hirurška resekcija sa VLE ostaje glavni standard u lečenju ove agresivne bolesti koja ima kraće ukupno preživljavanje. Melanom sluzokože koji nastaje u zidovima vagine je često klinički teže dijagnostikovana lezija, tako da je brza biopsija, pravovremena i tačna dijagnoza od presudnog značaja.

- Ključne reči: melanom vagine, melanociti, mukozalni melanom

Introduction

Primary vaginal melanoma (PVM) arises from aberrant melanocytes, whose precursors have migrated during gastrulation from the neural crest to the ectodermal mucosa (1). It is a rare type of mucosal melanoma that constitutes 0,3%–0,8% of all melanomas in women, and less than 3% of vaginal malignancies (2). PVM can appear as a pigmented plaque, ulceration, amelanotic lesion, or can be multifocal in 20% of the cases, with the most common localization on the anterior wall in the lower third of the vagina (3). It usually occurs in postmenopausal women, with a median age ranging from 54 to 76 years (4).

The clinical outcome remains poor with a 5-year overall survival (OS) 13-32.3% (5). Local surgical resection with clear margins is fundamental while adjuvant local radiotherapy has only impact in local disease control. No evidence based medical treatment in adjuvant or in systemic spread may be recommended. Nevertheless, immune-check inhibitors became a justified systemic treatment paradigm regarding their documented clinical benefit in other mucosal melanoma, while target therapies are much less effective (6).

Case Report

A 78-year-old female had complaints of a vaginal tingling,vaginal watery discharge, and dysuria for 4 months with a slowly increasing frequency over time.

The visual examination of the vulva did not show skin lesions.The combined vaginal speculum examination and vaginal palpation revealed a polypoid blackish growth arising from the anterior wall in the lower third of the vagina measuring 2,5x2 cm (Figure 1). The tumor mass with a smooth surface was associated with vaginal discharge and without bleeding. The other parts of the vaginal walls and uterine cervix were unremarkable. The bimanual palpation disclosed a mobile cervix without parametrium thickening and the uterus in anteversion and anteflexion was normal in size. Fallopian tubesand ovaries could not be palpated. The rectal examination revealed no abnormalities in the Douglas cavity.

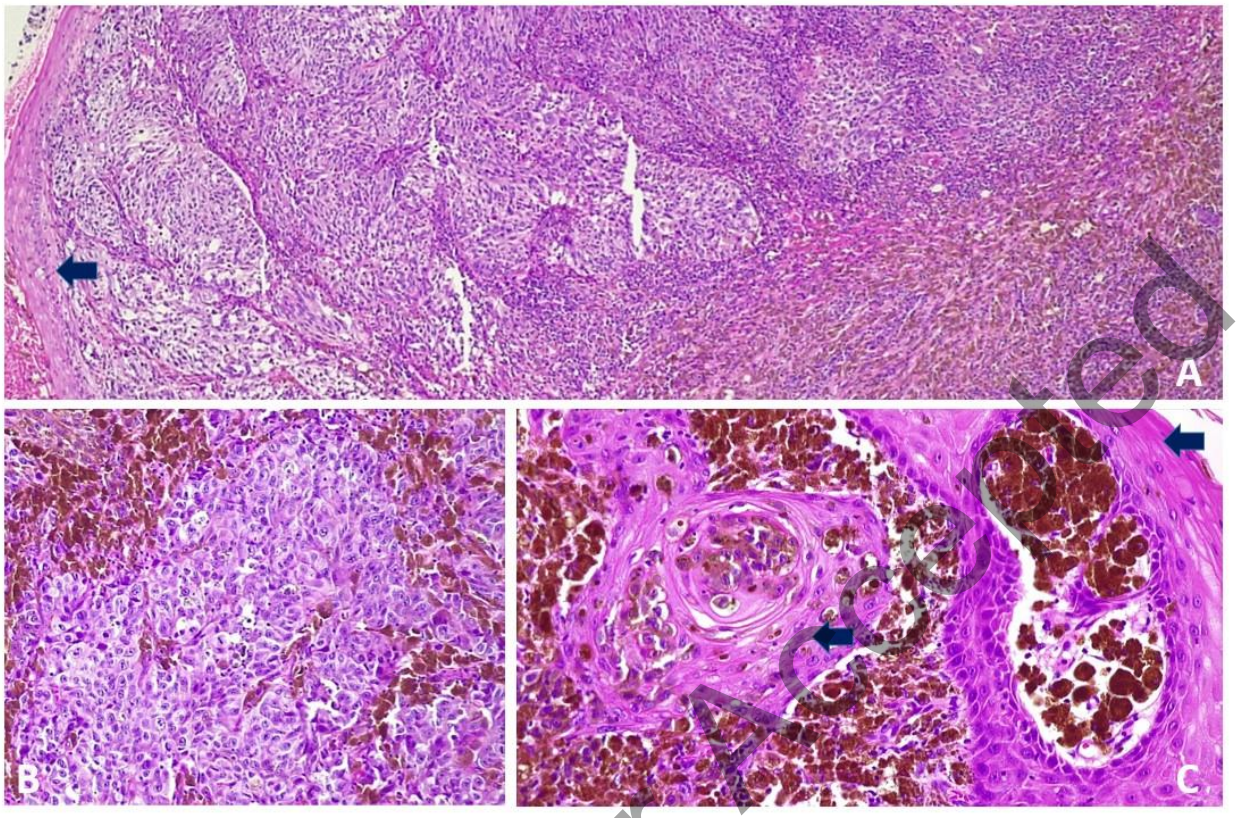

Figure 1. Micromorphology of primary vaginal melanoma. A) Vaginal neoplasm is composed of alveolar nests of spindled and epithelioid tumor cells, with wide ulceration of the overlying squamous epithelium. Squamous epithelium is marked by arrow. B) Tumor cells show variable degree of atypia and melanin pigment content. Note the large, epithelioid melanocytes with amelanotic cytoplasm admixed with heavily pigmented cells. C) Melanocytic proliferation shows pagetoid involvement of the squamous epithelium.

The incisional biopsy was performed and the histopathology analysis showed mucosal melanoma diagnosis (Figure 1). Immunohistochemically, the tumor cells were strongly positive for the SOX10, HMB-45, and S100 protein (Figure 2).

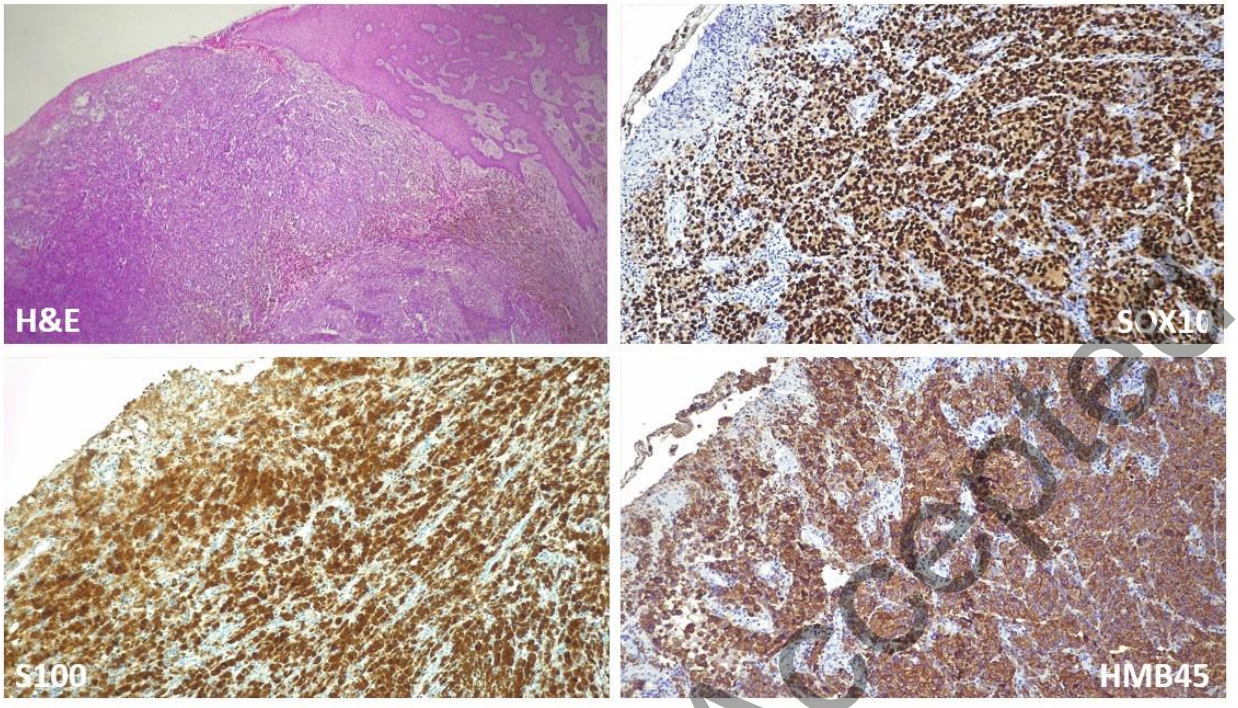

Figure 2. Immunophenotype of primary vaginal melanoma. Strong and diffuse expression of markers SOX10, S100, and HMB45 confirmed the melanocytic differentiation of both pigmented and non-pigmented tumor cells.

A complete clinical evaluation was done following the histopathological diagnosis. The computed tomography (CT) of the abdomen and the lesser pelvis, as well as chest x-ray, showed no evidence of the metastatic disease. The laboratory blood and urine tests were also in the normal range. Bilateral iliac, neck and axillary LNs showed no signs of enlargement.

The multidisciplinary team suggested dermoscopy and cystoscopy before the surgical removal of the tumor. An extensive evaluation did not detect any suspicious hyperpigmented skin or urinary tract mucosa llesions and the patient underwent the complete tumor excision without the SLN biopsy.

The tumor surface was without visible ulceration on gross findings. The cut surfaces were homogenous and dark-colored on serial sections.All tissue samples were processed by standard techniques, cut in 4-μm–thick sections, and stained with hematoxylin-eosin.

The histopathological analysis of the whole tumor showed epithelioid and spindled melanoma cells in the vertical (invasive) growth phase with no evidence of the preceding radial growth (Figure 1). Most of the tumor cells contained a dark-brown intracellular pigment. Superficial microscopic ulceration was present.The Breslow tumor thicknesswas 12 mm. The tumor-infiltrating lymphocytes (TILs) were non-brisk and the mitotic rate was 15 mitotic figures per $1mm^2$. Lymphovascular invasion was positive. Perineural and intraneural infiltration was not noticed. Tumor regression and the microscopic satellites were absent. The deep resection marginwas free of the tumor cells. According to the AJCC8^{th}stage grouping for melanoma, this case was of stage IIC (T4b, N0, M0).

Adjuvant therapy with either pembrolizumab or nivolumab for 12 months should be considered for patients with stage IIB-IIC disease. (ESMO 2025) 7-13

Discussion

The mucosal melanomas belong to a broad group of extracutaneous melanomas. Melanoma primary arising on the mucosal surfaces comprises head and neck, anorectal, urinary tract, and vulvovaginal melanoma, all representing aggressive tumors associated with difficult clinical diagnosis, due to their often obscure localization. Upon the biopsy of the suspicious lesion, pathological diagnosis often requires adjuvant diagnostic tools, usually immunohistochemical analysis of S100 protein, SOX10 and HMB-45, to confirm the melanocytic nature of the lesions. PVM are the most commonly ulcerated forms with a pronounced mitotic activity. In the case described herein, the localization on the anterior wall of the distal vaginal part, as well as histologic characteristics, epithelioid melanoma cell morphology, vertical growth, and high mitotic count, were typical features, in accordance with previously described findings (14,15).

The histopathological parameters necessary to determine the stage of the disease and the prognostic profile of melanoma are Breslow melanoma thickness, ulceration, microsatellite metastases / transient metastases, the number of mitoses, Clark invasion level (Chungmodification of the invasion of mucosal melanoma), tumor-infiltrating lymphocytes – TILs, lymphovascular invasion, neurotropism, resection margin status, the presence and the extent of regression (16). However, mucosal melanomas have a significantly worse clinical outcome compared to the

cutaneous counterparts, and there are no standardized protocols for determining histopathological prognostic parameters in primary mucosal melanomas. Improved understanding of the mucosal melanoma indicates that traditionally established histologic parameters, such as tumor thickness and presence of ulceration, do not correlate so well with the prognosis of the mucosal disease, as it does in skin lesions (17). Moreover, molecular analyses revealed that mucosal melanoma is rarely associated with BRAF mutations, which are often detected in cutaneous neoplasms. The most common genetic alterations in primary mucosal melanoma, including vulvo-vaginal cases, are activating mutations of the cell surface receptor tyrosine kinase C-KIT (14,17) and particularly SF3B1 (18,19).

The standard approach for the treatment of vaginal melanoma is surgery. Wide local excision or total vaginectomy or total hysterectomy with vaginectomy and vulvectomy and the observation of the regional lymph nodes with lymphadenectomy are applied if aSLN biopsy is positive (20, 21). WLE with the surgical safety margin of 1 cm is executed for tumors with a Breslow depth of 2 mm or less and 2 cm for the tumors with a Breslow depth of more than 2 mm with pelvic radiotherapy (21). The protocol of the European Organization for Research and Treatment of Cancer (EORTC) involves the intersection of SLNs along the longitudinal axis and examination of both halves on hematoxylin-eosin (HE) and immunohistochemically stained preparations (22).-The revised American Joint Committee on Cancer (AJCC) 2017 staging system is used in vaginal melanoma including tumor thickness, regional lymph nodes (LN) involvement, and distant metastases, although some authorsconsider a tumor size (<3cm versus ≥3cm) to be an important predictor of prognosis (23). The recommended treatment is a wide local excision (WLE) with adequate margins (clinical 1 cm circumferentially), while radical procedures (vaginectomy, pelvic exenteration) may be considered depending on the tumor location (6). Sentinel lymph node (SLN) biopsy is challenging in vaginal melanoma, but the excision of clinically or radiologically suspicious LNs is rather suggested (24). The positive role of adjuvant radiotherapy has been suggested by the studies in patients with no clear surgical margins, whose tumor size was more than 3cm or had positive groin or pelvic nodes and definitive primary treatment, then in the patients with surgically unresectable disease or in the patients who refused surgery. However, the role of radiotherapy remains only in a term of local control while no observation have been documented

in a term of systemic disease control (12). Regarding systemic treatment for mucosal melanomas, including PVM, immunotherapy with pembrolizumab, nivolumab and ipilimumab are evidence based options (19-24). Targeted therapies may be a part of systemic treatment if specific activation mutation has been detected (c-kit, BRAF/MEK, N/K-RAS or others) with variable potential of efficacy.

Conclusion

Surgical resection with WLE remains the mainstay in the treatment of this aggressive disease with poor OS. Mucosal melanoma that arises in vaginal walls is often clinically indiscernible lesion, thus prompt biopsy, timely and accurate diagnosis is of crucial significance.

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