Case report

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PRIMARY VAGINAL MELANOMA

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Primary vaginal melanoma is a rare type of mucosal melanoma accounting for 0.3% to 0.8% of all melanomas in women and less than 3% of all vaginal malignancies.

A 78-year-old female presented with complaints of vaginal tingling, vaginal watery vaginal discharge, and dysuria lasting for four months, with a gradual increase in symptom frequency over time. The patient underwent complete tumor excision. Immunohistochemical analysis showed that the tumor cells were strongly positive for SOX10, HMB-45, and S100 proteins. Histopathological examination of the entire tumor revealed epithelioid melanoma cells in the vertical (invasive) growth phase with no evidence of a preceding radial growth phase. Most tumor cells contained dark-brown intracellular pigment. Superficial microscopic ulceration was present. The Breslow tumor thickness was 12 mm. Tumor-infiltrating lymphocytes were non-brisk, and the mitotic rate was 15 mitoses per mm^2. Lymphovascular invasion was present, while perineural and intraneural infiltration were not noticed. Tumor regression and microscopic satellites were absent. The deep resection margin was free of tumor cells. According to the AJCC 8th edition melanoma staging system, the tumor was classified as stage IIC (T4b, N0, M0).

Surgical resection with wide local excision remains the mainstay in the treatment of this aggressive disease with poor overall survival. Mucosal melanoma arising in the vaginal wall is often clinically indiscernible; therefore, prompt biopsy and timely, accurate diagnosis are of crucial importance.

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Key words: *vaginal melanoma, melanocytes, mucosal melanomas*

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Introduction

Primary vaginal melanoma (PVM) arises from aberrant melanocytes, whose precursors migrate during gastrulation from the neural crest to the ectodermal mucosa (1). It is a rare type of mucosal melanoma, accounting for 0.3%–0.8% of all melanomas in women and less than 3% of vaginal malignancies (2). Primary vaginal melanoma may present as a pigmented plaque, ulceration, or amelanotic lesion, and may be multifocal in approximately 20% of cases. The most common localization is on the anterior wall in the lower third of the vagina (3). It predominantly 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 rate of 13–32.3% in patients (5). Surgical resection with clear margins is fundamental, while adjuvant radiotherapy contributes to local disease control. Currently, there is no established evidence-based systematic therapy recommended in either the adjuvant setting or for metastatic disease.

Nevertheless, immune checkpoint inhibitors have emerged as a justified systemic treatment option, regarding their documented clinical benefit in other mucosal melanomas, while targeted therapies are much less effective (6).

Case Presentation

A 78-year-old female presented with complaints of vaginal tingling, watery vaginal discharge, and dysuria lasting for four months with a gradual increase in symptom frequency over time.

Visual examination of the vulva revealed no skin lesions. Combined vaginal speculum examination and palpation identified a polypoid,

blackish lesion arising from the anterior wall in the lower third of the vagina, measuring 2.5 x 2 cm (Figure 1). The tumor mass had a smooth surface and was associated with vaginal discharge, without bleeding. The remaining parts of the vaginal walls and uterine cervix were unremarkable. Bimanual examination disclosed a mobile cervix without parametrium thickening, while the uterus was in anteversion and anteflexion and normal in size. The fallopian tubes and ovaries were not palpable. Rectal examination revealed no abnormalities in the Douglas pouch.

An incisional biopsy was performed, and histopathological analysis confirmed the diagnosis of mucosal melanoma (Figure 1). Immunohistochemical analysis demonstrated strong positivity of tumor cells for the SOX10, HMB-45, and S100 proteins (Figure 2).

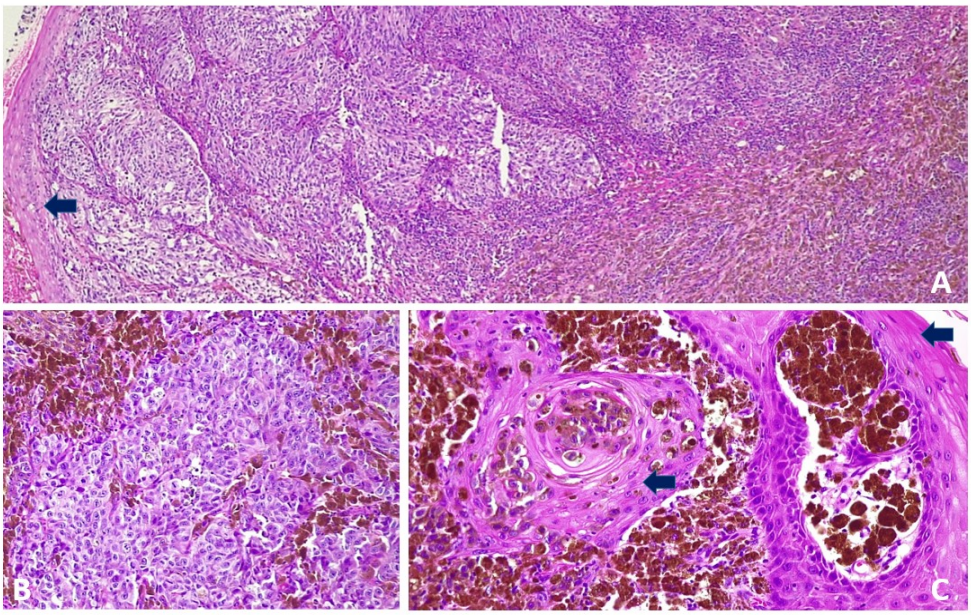

Figure 1. Micromorphology of primary vaginal melanoma. A) The vaginal neoplasm is composed of alveolar nests of spindled and epithelioid tumor cells, with extensive ulceration of the overlying squamous epithelium. The squamous epithelium is marked by an arrow. B) Tumor cells show a variable degree of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

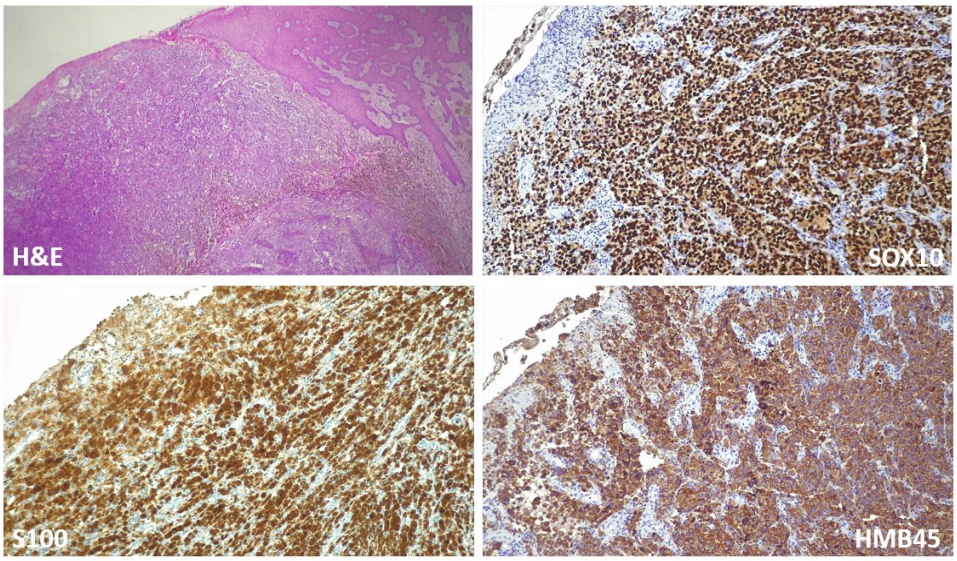

Figure 2. Immunophenotype of primary vaginal melanoma. Strong and diffuse expression of SOX10, S100, and HMB-45 confirms the melanocytic differentiation in both pigmented and non-pigmented tumor cells.

A complete clinical evaluation was performed following the histopathological diagnosis. Computed tomography of the abdomen and pelvis, as well as chest radiography, showed no evidence of metastatic disease. Laboratory blood and urine tests were also within normal limits. Bilateral iliac, cervical, and axillary lymph nodes showed no evidence of enlargement.

The multidisciplinary team suggested dermoscopic examination and cystoscopy before the surgical tumor removal. Extensive evaluation did not detect any suspicious hyperpigmented skin or urinary tract mucosal lesions, and the patient underwent complete tumor excision without the sentinel lymph node (SLN) biopsy.

Gross examination revealed no visible ulceration on the tumor surface. The cut surfaces were homogeneous and dark-colored on serial sectioning. All tissue samples were processed using standard techniques, cut into 4-μm sections, and stained with hematoxylin and eosin.

Histopathological analysis of the entire tumor revealed epithelioid and spindled melanoma cells in the vertical (invasive) growth phase with no evidence of the preceding radial growth phase (Figure 1). Most tumor cells contained dark-brown intracellular pigment. Superficial microscopic ulceration was present. The Breslow tumor thickness was 12 mm. Tumor-infiltrating lymphocytes (TILs) were non-brisk, and the mitotic rate was 15 mitoses per mm^2. Lymphovascular invasion was present, while perineural and intraneural infiltration were not noticed. Tumor regression and the microscopic satellites were absent. The deep resection margin was free of tumor cells. According to the AJCC 8th edition melanoma staging system, the tumor was classified as stage IIC (T4b, N0, M0).

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

Discussion

Mucosal melanomas belong to a heterogeneous group of extracutaneous melanomas. Primary melanomas arising on the mucosal surfaces include those of the head and neck, anorectal region, urinary tract, and vulvovaginal area, all of which are aggressive tumors associated with challenging clinical diagnosis due to their often inconspicuous localization. Following biopsy of a suspicious lesion, pathological diagnosis often requires adjuvant diagnostic methods, most commonly immunohistochemical analysis of S100 protein, SOX10, and HMB-45, to confirm the melanocytic nature of the lesions. Primary vaginal melanomas are among the most frequently ulcerated forms with a pronounced mitotic activity. In the present case, tumor localization on the anterior wall of the distal vagina, along with histological features such as epithelioid cell morphology, vertical growth phase, and high mitotic rate, are consistent with previously described findings (14, 15).

Histopathological parameters necessary to determine the stage of the disease and the prognostic profile of melanoma include Breslow melanoma thickness, ulceration, microsatellite metastases or in-transient metastases, mitotic rate, Clark level of invasion (Chung modification for mucosal melanoma), TILs, lymphovascular invasion, neurotropism, resection margin status, and the presence and extent of tumor regression (16). However, mucosal melanomas are associated with a significantly poorer clinical outcome compared to their cutaneous counterparts, and there are no standardized protocols for assessing histopathological prognostic parameters in primary mucosal melanomas. Improved understanding of mucosal melanoma indicates that traditionally established histologic parameters, such as tumor thickness and ulceration, correlate less strongly with prognosis in mucosal melanoma than in cutaneous melanoma (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 vulvovaginal cases, involve activating mutations in the receptor tyrosine kinase c-KIT (KIT) and, particularly, in SF3B1 (14, 17–19).

The standard approach to the treatment of vaginal melanoma is surgical resection.

Wide local excision (WLE), total vaginectomy, or total hysterectomy with vaginectomy and vulvectomy may be performed depending on tumor extent and location. Assessment of regional lymph nodes (LNs) is recommended, with lymphadenectomy indicated in cases of a positive sentinel lymph node (SLN) biopsy (20, 21). Wide local excision with the surgical safety margin of 1 cm is executed for tumors with a Breslow thickness of ≤ 2 mm, and 2 cm for tumors > 2 mm, with consideration of adjuvant pelvic radiotherapy (21). The European Organization for Research and Treatment of Cancer protocol includes longitudinal sectioning of SLNs and examination of both halves using hematoxylin and eosin staining and immunohistochemistry (22). The revised American Joint Committee on Cancer staging system 2017 is applied in vaginal melanoma and incorporates tumor thickness, regional LNs involvement, and distant metastases. However, some authors suggest that tumor size (< 3 cm vs. ≥ 3 cm) may also serve as an important prognostic factor (23). The recommended treatment is a WLE with adequate margins (approximately 1 cm circumferentially), while radical procedures (e.g., vaginectomy or pelvic exenteration) may be considered based on tumor location (6). Sentinel lymph node biopsy is challenging in vaginal melanoma, but the excision of clinically or radiologically suspicious LNs is rather suggested (24). Adjuvant radiotherapy may be considered in patients with positive or close surgical margins, tumor size > 3 cm, nodal involvement, or unresectable disease, as well as in

those who are not candidates for surgery. However, radiotherapy primarily contributes to local disease control, with no clear evidence supporting its role in systemic disease control (12). Regarding systemic treatment, immunotherapy with pembrolizumab, nivolumab, or ipilimumab is an evidence-based option for mucosal melanomas, including PVM (19–24). Targeted therapies may be considered in selected cases with identified activating mutations (e.g., c-KIT, BRAF/MEK, or NRAS), although their efficacy remains variable.

Conclusion

Surgical resection with a WLE remains the mainstay of treatment for this aggressive disease, which is associated with poor overall survival. Vaginal mucosal melanoma that arises in vaginal walls is often clinically inconspicuous; therefore, prompt biopsy and timely, accurate diagnosis are of crucial significance.

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Prikaz slučaja

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PRIMARNI MELANOM VAGINE

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

Sedamdesetosmogodišnja žena je kao tegobe navela peckanje u vagini, vodenasti iscedak iz vagine i dizuriju, napominjući da je u poslednja četiri meseca to postalo češće. Pacijentkinji je urađena potpuna ekscizija tumora. Tumorske ćelije su imunohistohemijski 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 sadržala je tamnobraon intracelularni pigment, a zabeleženo je i prisustvo površinske mikroskopske ulceracije. Debljina tumora je iznosila 12 mm. Mitotička stopa je bila 15 mitotičkih figura po 1 mm^2, sa limfovaskularnom invazijom koja je bila pozitivna. Nisu primećene ni perineuralna ni intraneuralna infiltracija. Nije bilo ni regresije tumora ni mikroskopskih satelita. Na margini duboke resekcije nije bilo tumorskih ćelija. Prema grupi AJCC 8. stadijuma za melanom, ovo je bio slučaj stadijuma IIC (T4b, N0, M0).

Hirurška resekcija za koju se koristi VLE (engl. *volumetric laser endomicroscopy* – VLE) ostaje glavni standard u lečenju ove agresivne bolesti, kod koje je ukupno preživljavanje pacijentkinja kraće. Melanom sluzokože koji nastaje u zidovima vagine često je klinički teže dijagnostikovana lezija, tako da su brza biopsija i pravovremena i tačna dijagnoza od presudnog značaja.

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***Ključne reči**: melanom vagine, melanociti, mukozalni melanom*