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Vaginal epithelioid malignant peripheral nerve sheath tumor nearly misdiagnosed as advanced cervical cancer: A case report

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ABSTRACT

A 56-year-old woman was referred to our hospital with a pathological diagnosis of squamous cell carcinoma of the cervix. We performed a re-biopsy of the vaginal mass and cervical conization. The mass was originally reported as an epithelioid MPNST after re-biopsy. Strong diffuse S-100 positivity, epithelioid morphology of the lesion, and negativity to all other immune histochemical markers confirmed the diagnosis of epithelioid MPNST. Cervical conization specimen was negative for any neoplasms.

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1. Introduction

Primary vaginal cancer is a rare entity and represents only 1%–2% of malignant neoplasms of the female genital tract [1]. Approximately 90% of primary vaginal cancers are squamous cell type carcinomas. Mesenchymal tumors of the vagina originate from the stroma or associated elements (e.g., connective tissue, vascular, or neural structures) and are extremely rare [2]. In contrast, benign mesenchymal tumors of the vagina (i.e., fibroepithelial polyp, angioma fibroblastoma, postoperative spindle cell nodule, nodular fasciitis, dermatofibroma, leiomyoma, rhabdomyoma, and granular cell tumors) are relatively common. The malignant mesenchymal tumors (e.g., aggressive angiomyxoma, leiomyosarcoma, proximal epithelioid sarcoma, rhabdomyosarcoma and Liposarcomatous differentiation,) are much rarer [2–17].

Schwannomas are benign soft tissue tumors of neural origin, and the majority of the vaginal schwannomas have been previously reported in case series as a benign condition. Malignant form of schwannoma has been recently defined as malignant peripheral nerve sheath tumor.

Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon, biologically aggressive tumors constituting up to 5% of all soft tissue sarcomas; it is even rarer in the female genital region (i.e., the cervix, uterus, vulva, and vagina) [3]. Furthermore, an epithelioid malignant peripheral nerve sheath tumor is an extremely rare variant of MPNST. In this study, we report the first case of vaginal epithelioid MPNST.

2. Case presentation

A 56-year old woman (gravida II, para II) was admitted to a secondary healthcare center with a three-month history of an abnormal bloody vaginal discharge. After a cervical and vaginal mass biopsy had been attempted, she was referred to our hospital with a pathologic diagnosis of squamous cell carcinoma of the cervix (large cell nonkeratinizing type) and a vaginal mass with chronic inflammation and edematous cellular change. Human papilloma virus (HPV) testing was reported negative for a high-risk strain.

She had a history of two spontaneous vaginal deliveries and no family history of cancer or any hereditary disease. She did not exhibit café-au-lait spots on her skin or neurofibromatosis. A physical examination with a speculum revealed a mass of approximately 3 cm in diameter originating from the lower portion of the left vaginal wall. The tumor had a yellow-reddish appearance and a rubber consistency. We performed a biopsy on the vaginal

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Fig. 1. Gross pathological specimen of the vaginal mass excision.

mass and endometrial, endocervical curettage. For the preoperative evaluation, she was referred to the radiology department for lower abdominal magnetic resonance imaging (MRI) and computed tomography (CT). We planned to perform a radical hysterectomy as well as pelvic and para-aortic lymphadenectomy for cervical cancer as reported previously, following these procedures. However, we had to postpone the surgery due to obscure pathologic findings of the biopsy samples and re-biopsy proposal in the pathology report. Counseling with the patient regarding treatment was performed and informed, written consent was obtained. We removed the vaginal mass via the vaginal route and performed a cold-knife cervical cone biopsy. The patient's vaginal tumor was originally reported as an epithelioid malignant peripheral nerve sheath tumor by our pathology department after the large excisional mass biopsy procedure.

3. Surgical findings

The patient was prepared for surgery following our routine preoperative procedures. The large, polypoid mass was protruding from the left vaginal wall into the vaginal cavity. The vaginal tumor was removed circumferentially with the deep vaginal mucosa widely at least 2 cm healthy tissue. Upon gross examination, the tumor revealed a yellow-reddish appearance without necrosis, with an irregular surface measuring $3 \times 4 \times 2$ cm (Fig. 1). We also performed a large cold-knife cervical cone biopsy with an additional endocervical canal curettage. The patient's postoperative period was uneventful, and there were no perioperative complications.

4. Radiologic imaging findings

MRI was performed using a 1.5 T superconducting magnet. The MRI revealed a $16 \times 23 \times 32$ mm diameter tumor in the left side of half of the proximal portion of the vaginal wall. The lesion generated a low signal on the T1-weighted spin-echo (SE) images and a high signal on the T2-weighted SE images (Fig. 2a and b). On the post-contrast T1 weighted images, the lesion infiltrating into the lower vaginal mucosa exhibited homogenous enhancement and the edges of the mass showed continuity with the anterior vaginal mucosa. There were no mass images found in the cervix. On the CT scan, there was no evidence of lymphadenopathy or distant metastases.

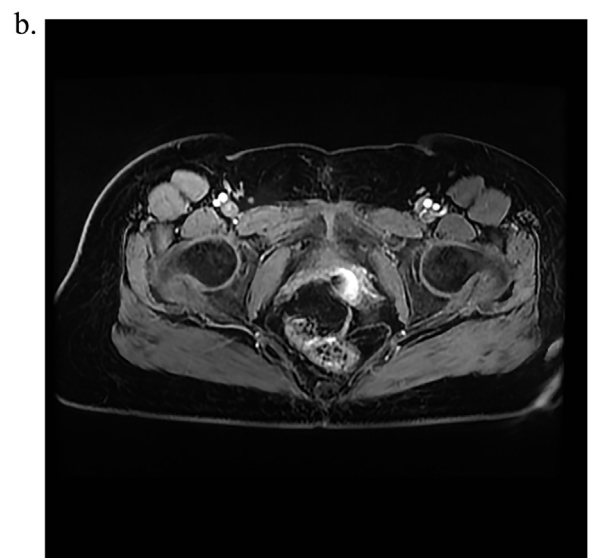
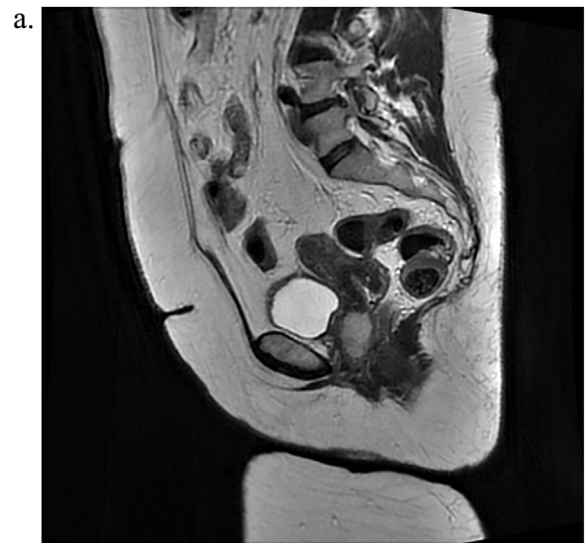


Fig. 2. Magnetic resonance images. a) Sagittal T2-weighted image reveals a high-intensity oval tumor $16 \times 23 \times 32$ cm in the vaginal wall. b) Axial T2 weighted image shows a high-intensity tumor in the left vaginal wall.

5. Pathological findings

5.1. Macroscopically

The vaginal lesion was a $3 \times 2 \times 2,5$ cm elastic mass of a tan, flesh-colored with a homogenous cut surface and rubbery consistency. Hemorrhage and necrosis were not observed. While one surface of the lesion was regular and polypoid, the other surface was irregular. The irregular surface was inked with blue dye, and the lesion was completely sampled. Cervical conization material was a $15 \times 10 \times 0,5$ mm mass of a tan-colored homogenous cut surface. It was also entirely sampled. There was no gross lesion found on the conization material macroscopically.

5.2. Microscopically

Upon microscopic examination of vaginal mass, there was a lesion just beneath the benign squamous epithelium without a grenz zone with alternating hypo- and hypercellular areas. The regions just beneath the squamous epithelium were hypocellular, while deep areas were hypercellular. The lesion was composed of

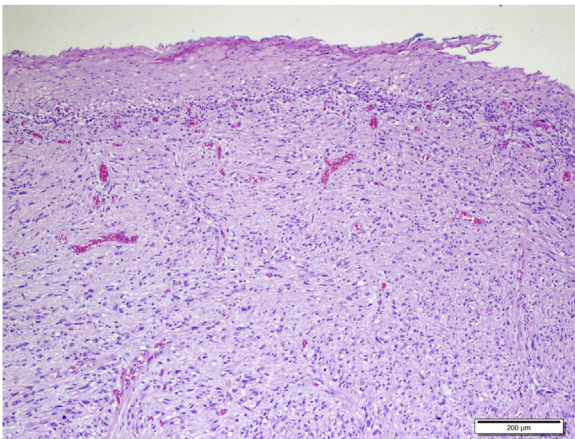


Fig. 3. Vaginal mass exhibiting a spindle to epitheloid morphology beneath the benign squamous epithelium (hematoxylin and eosin; original magnification 40×).

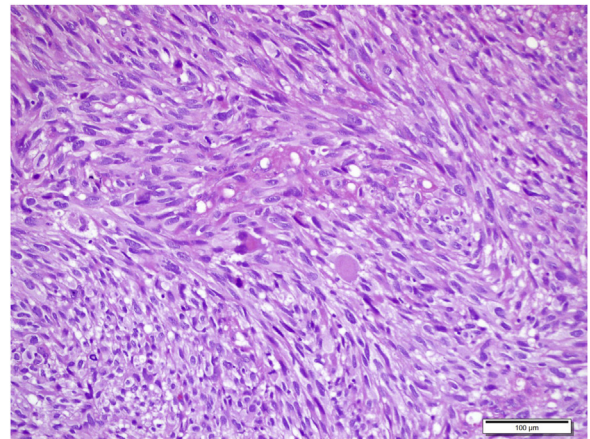


Fig. 5. Spindle to epitheloid cells, marked pleomorphism, and abundant mitotic figures (hematoxylin and eosin; original magnification 200×).

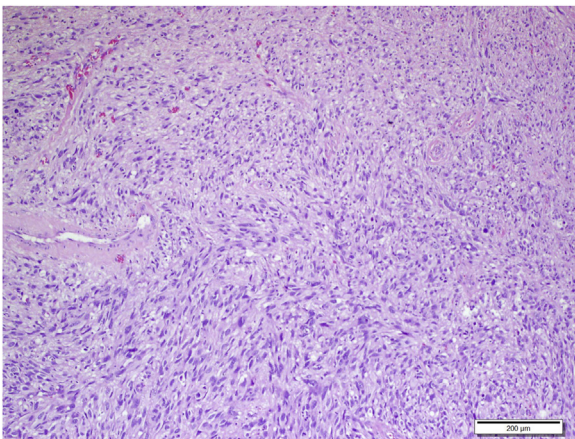


Fig. 4. The tumor is composed of pleomorphic spindle to epitheloid cells with an abundant eosinophilic cytoplasm and a hyperchromatic vesicular nucleus with conspicuous nucleoli (hematoxylin and eosin; original magnification 100×).

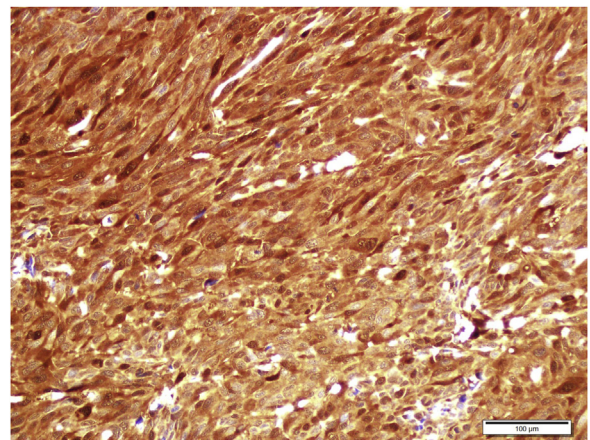


Fig. 6. Diffuse strong immunostaining of the tumor cells with the S-100 antibody (S-100 immunostain; original magnification 200×).

spindle to pleomorphic epitheloid cells arranged in a fascicular pattern in some areas and disorganized in other areas. The tumor cells had indistinct cell borders and an abundant eosinophilic granular cytoplasm. The nuclei of the tumor cells were hyperchromatic with vesicular chromatin and a conspicuous nucleoli. Mitoses with abnormal mitotic figures were abundant within the lesion (Figs. 3, 4, and 5). The cervical conization material revealed regular squamous epithelium and stroma without any dysplastic changes.

Microscopically, tumor necrosis or angiolymphatic invasion was not identified, and the vaginal tumor specimen had negative margins. The tumor with MPNST was confined to the vaginal wall, and the endocervical curettage was negative for any neoplasms.

5.3. Immunohistochemically

The tumor cells were immunonegative for all epithelial markers (e.g., PanCK, CK 5,6, HMWCK, EMA, and Cam 5.2; Fig. 7). There was no immunoreactivity with SMA, Desmin, or Caldesmon (Fig. 8). The tumor cells did not stain positive for antibodies against p63, p120, p16, ER, PR, CD 10, and Cyclin D1 (Fig. 7). Moreover, the tumor cells showed strong diffuse positive staining with Vimentin and S-100 (Fig. 6), but there was no immunoreactivity with HMBE-45, Melan-A (Fig. 9), or MDM 2. The proliferative activity with Ki-67 (Fig. 10) and PHH3 was very high.

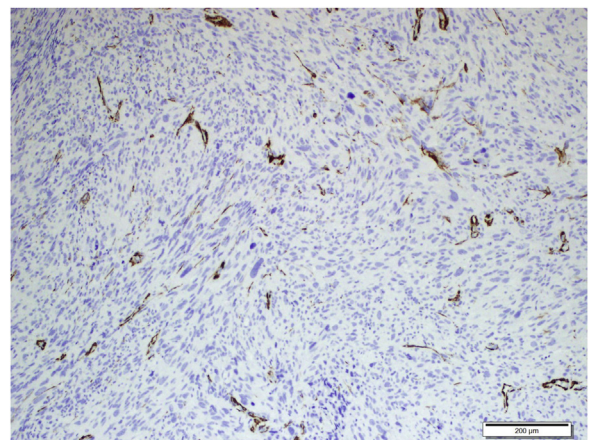


Fig. 7. Tumor cells were immunonegative for antibodies against Pan CK and p63 (Pan CK, p63 immunostain; original magnification 200×).

5.4. Differential diagnosis

As the patient’s lesion had a spindle to epitheloid morphology with no conspicuous epithelial component; spindle cell squamous cell carcinoma, leiomyosarcoma, malign mixed mullerian tumor, and stromal sarcoma were included in the initial differential diagnosis. The lesion was negative for all epithelial markers (e.g., Pan

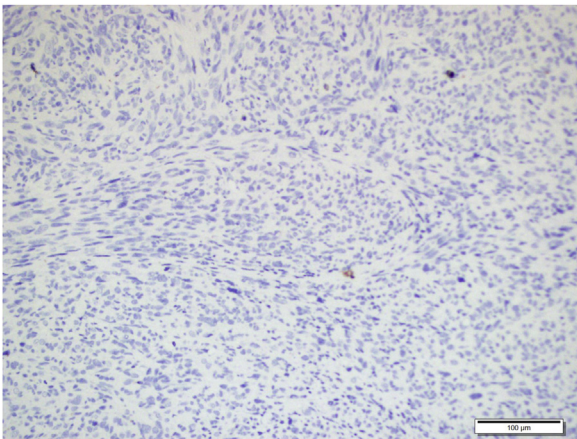


Fig. 8. Negative immunostaining of the tumor cells with antibodies against SMA and Desmin (SMA and Desminimmunostain; original magnification 200×).

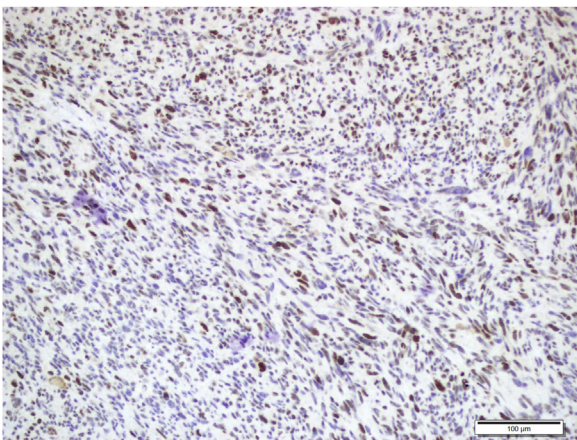


Fig. 9. Tumor cells were negative for the melanoma markers HMBE-45 and Melan-A (HMBE-45 and Melan-A immunostain; original magnification 200×).

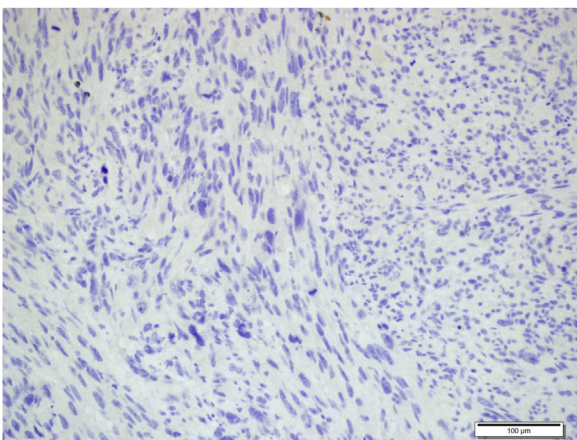


Fig. 10. Abundant mitotic activity and very high proliferative index of tumor cells (Ki-67 immunostain; original magnification 200×).

CK, EMA, Cam5.2, HMWCK, and p63). Together with these findings and the p16 immunonegativity, spindle cell squamous carcinoma was excluded. SMA, Desmin, Caldesmon immunonegativity also excluded leiomyosarcoma. Negative staining with antibodies to ER, PR, CD10, and Cyclin D1 excluded stromal sarcoma. According to diffuse and strong Vimentin and S-100 positivity; melanoma, malignant epitheloid nerve sheath tumor, liposarcoma and malig-

nant mixed mesodermal tumor with heterologous elements were considered. Due to melan-A and HMBE-45 negativity, melanoma was excluded, and MDM 2 negativity also excluded liposarcoma. Together with the diffuse strong s-100 positivity and epitheloid morphology, the lesion was considered to be epitheloid MPNST due to the negativity of all other immunohistochemical markers and the absence of any mass lesions in the endometrium.

6. Follow-up

In a five-year follow-up period we never encountered a negative situation or a relapse on physical examinations and radiological imagings.

7. Discussion

Schwannoma is a benign tumor of the peripheral nerves that arises from Schwann cells. These rare tumors occur in any nerve trunk or organ except the olfactory and optic nerves, which lack Schwann cells [4]. The most common locations for schwannomas are the upper extremities, trunk, head, and neck. Vaginal schwannoma likely arises from the branches of the inferior hypogastric nerve plexus or pudendal nerves.

A malignant peripheral nerve sheath tumor is referred to as a malignant schwannoma, neurogenic sarcoma, or neurofibrosarcoma. However, since these terms have been previously ill-defined, they have been recently replaced with MPNST [5]. We searched for the terms vaginal malignant schwannoma, neurogenic sarcomas, neurofibrosarcoma, or malignant peripheral nerve sheath tumor in PubMed, Google Scholar (<https://scholar.google.com.tr>), and the Turkish National Database of Science and Technology (<http://uvt.ulakbim.gov.tr/uvvt/>). Our search revealed two cases. The first was reported as 22-year woman with a 10 cm malignant schwannoma in 1976 [6]. The second was identified as neurofibrosarcoma by the title “Primary Sarcoma of the Adult Vagina: A Clinicopathologic Study” [7]. Therefore, the case presented in this report is only the third reported case of malignant vaginal schwannoma and is the first vaginal epitheloid malignant nerve sheath tumor in the literature.

MPNSTs comprise ~2% of all sarcomas. The malignant transformation of schwannomas is a rare occurrence, and the tumor cells typically transform into either high-grade malignant epitheloid cells or a malignant “small cell neuroepithelial” tumor [4]. Epitheloid MPNST is an extremely rare variant of MPNST (less than 5% of all cases), and it is composed of plump, epitheloid cells with an abundant eosinophilic cytoplasm and typically demonstrate lobulated growth. Immunohistochemically, MPNST is positive for S-100 protein in <50% of cases, and staining is generally focal. Diffuse staining is rarely observed in conventional MPNST and should raise the risk of developing other tumors (e.g., melanoma); however, in contrast with conventional MPNST, epitheloid MPNST is strongly and diffusely positive for S-100 [5,8].

MPNST may arise at any age with no gender predilection. However, the median age for sporadic MPNST is between 30 and 60 years, and NF1-associated MPNST tends to have a younger age of onset (20–40 years) [9,10]. The clinical presentation of vaginal schwannomas may be pain, especially if it is a large mass and can be combined with vaginal bleeding or discharge from the vagina as in this case, or it can also be asymptomatic [11,12].

Surgery is the primary method of treatment, and a complete excision with free margins is essential. The prognosis of malignant schwannomas is poor. The most important prognostic factor of MPNST was reported to be the presence of neurofibromatosis, a tumor size >5 cm, and the extent of the resection. The epitheloid malignant change has no prognostic significance if there is no

transcapsular invasion. Survival was improved by a total resection; however, adjuvant radiation or chemotherapy did not affect survival. The overall five- and ten-year survival rates were 34% and 22%, respectively [6,13,14].

MPNST is extremely rare in the female genital region as the cervix, uterus, vulva, and vagina. In the literature, eight cases of MPNST of the uterine cervix were reported, seven of which were treated via a hysterectomy. A 22-year-old woman was managed with a radical trachelectomy because of her desire to conserve her fertility [15].

A malignant vaginal schwannoma 10 cm in diameter from a 22-year-old woman was presented by Davos et al. [6]. The neoplasm was locally excised and recurred five times on adjacent soft tissues, but the resected pelvic lymph nodes were free of metastatic disease. Lymph node metastasis was not reported in the cases of MPNST located in the uterine cervix or vagina [6,15].

In addition Vaginal Malignant Peripheral Nerve Sheath Tumor (MPNST) With Unusual Liposarcomatous Differentiation, 8.6 × 6.0 cm in diameter from a 70-year-old woman was presented F Gougeon et al. One of them showed cavitation. Two lymph nodes adjacent to the left iliac vessels were suspicious for metastasis. There was no evidence of extra-nodal metastatic disease. The patient underwent a surgical biopsy of one of the vaginal masses. The diagnosis of MPNST, epithelioid variant with liposarcomatous differentiation, grade 3/3 was made and confirmed by a pathologist specialized in soft-tissue tumors. The patient was offered neo-adjuvant radio-chemotherapy and surgery but chose a palliative approach [17].

This supports the prevailing recommendation that to remove the tumor with a wide excision is enough to cure MPNST. Subsequently, there is no need to perform pelvic lymphadenectomy or any other procedure.

Approximately 80% of vaginal cancers are metastatic, primarily from the cervix or endometrium [16], which is one of the possible reasons that there was a diagnostic challenge in the present case. Furthermore, MPNSTs could be misdiagnosed due to rarity. We consider that the recognition of this rare entity requires high specialty. In this case, the diagnosis was changed from squamous cell cervical cancer to an epithelioid malignant peripheral nerve sheath tumor after the subsequent excisional mass biopsy. This manuscript has been written in accordance with the SCARE guideline rules [18].

8. Conclusion

Differential diagnosis between MPNSTs and other tumors localized in the same site is particularly important, as in the present case. Therefore, MPNST must be considered in the differential diagnosis.

Declaration of Competing Interest

There is no conflict of interest

Funding

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Ethical approval

This manuscript is a case report. So there is no ethical approval

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy

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