Thieme

Malignant Peripheral Nerve Sheath Tumor (MPNST) of the Uterine Cervix – A Systematic Literature Review and New Case Report with Possible New Therapeutic Approaches

Maligner peripherer Nervenscheidentumor (MPNST) des Cervix uteri – ein systematischer Literaturüberblick und neuer Fallbericht mit potenziellen neuen Therapieansätzen

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ABSTRACT

Malignant schwannomas of the visceral organs are extremely rare. To date, 19 cases of cervical schwannoma have been reported in the literature worldwide. A single case prompted a review of the literature. The differential diagnosis between melanoma and schwannoma is made using the marker HMB-45, which is positive for melanoma and negative for schwannoma. This differentiation allowed us to identify two of the 20 cases that were probably not schwannomas.

The prognosis of malignant cervical schwannoma is poor. Approximately half of the cases develop local recurrence or distant metastases within a short time, despite resection in healthy tissue.

In one case, gene sequencing revealed a potential treatment approach with the mTOR inhibitor everolimus and trastuzumab. Unfortunately, the potential efficacy of these treatment options could not be tested because the patient was being treated at another hospital at the time of relapse, and they did not use a drug that matched the NGS profile.

ZUSAMMENFASSUNG

Maligne Schwannome der viszeralen Organe sind extrem selten. Bis heute gibt es weltweit nur 19 Fallberichte von zervikalen Schwannomen in der Literatur. Das Auftreten eines solchen Schwannoms in unserem Krankenhaus war der Anlass für eine Sichtung der aktuellen Literatur. Die Differenzialdiagnose unterschiedet zwischen einem Melanom und einem Schwannom mithilfe des Markers HMB-45, der positiv für Melanome und negativ für Schwannome ist. Diese Differenzierung erlaubte uns, aus 20 Fällen 2 zu identifizieren, die wahrscheinlich keine Schwannome waren.

Die Prognose für ein malignes zervikales Schwannom ist schlecht. In der Hälfte aller Fälle entwickelt sich innerhalb kurzer Zeit ein Lokalrezidiv oder eine Fernmetastase, selbst wenn die Resektion im gesunden Gewebe durchgeführt wurde.

In einem Fall hat die Genomsequenzierung einen möglichen Behandlungsansatz mit dem mTOR-inhibitor Everolimus und Trastuzumab aufgezeigt. Leider konnte die potenzielle Wirk-

samkeit dieser Behandlungsoption nicht geprüft werden, weil die Patientin zum Zeitpunkt des Rückfalls in einem anderen Krankenhaus behandelt wurde und das Krankenhaus kein Arzneimittel, das dem NGS-Profil entsprach, einsetzte.

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma that originates from the peripheral nerves or shows differentiation of various components of the nerve sheath, formerly known as neurogenic sarcoma, neurofibrosarcoma or malignant schwannoma. MPNST is a relatively rare spindle cell sarcoma that accounts for approximately 3% to 10% of soft tissue sarcomas. Nearly half of the cases are due to neurofibromatosis type 1 (NF 1), less than 10% are radiation-induced (post-radiotherapy sarcomas), and the remainder are sporadic cases of unknown etiology. Malignant schwannomas in parenchymal organs are very rare.

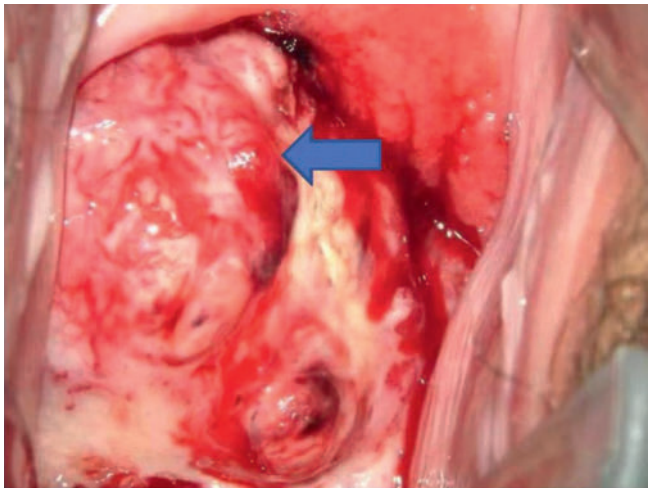
A recent case in our hospital with schwannoma of the cervix uteri prompted us to conduct an extensive literature search. The case reported here is the 18 th to be definitively confirmed worldwide. In the past, neither chemotherapy nor radiotherapy has been effective for malignant schwannomas. This is the first case in which advanced (next-generation) gene sequencing (NGS) has been used to better understand the biology of the tumor and identify potential treatment options in the event of recurrence. According to the literature, approximately half of these cases will experience recurrence, even when the tumor is removed with extensive resection in health tissue. The aim of this article is to report a significant clinical case and add to the available literature on cervical schwannoma.

Case Report with Next-generation Sequencing

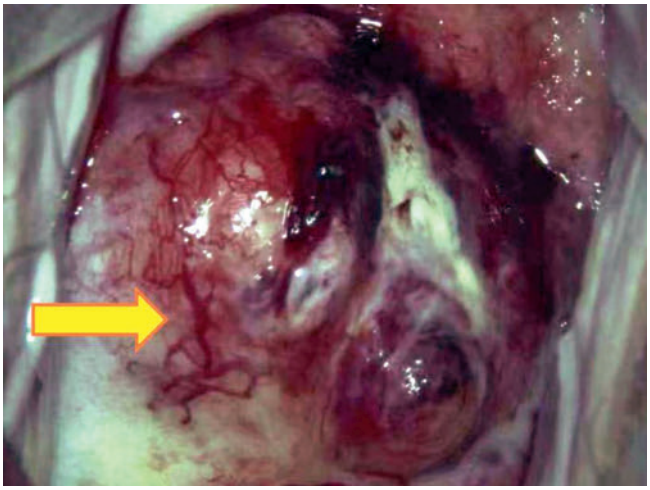
We report a case of malignant nerve sheath tumor of the cervix (MPNST). The patient, 29 years old, gravida 3 and para 1, presented with vaginal spotting for 2 months. She had a history of spontaneous vaginal delivery and no hereditary disease or other complaints. Her mother had a history of rectal cancer and her aunt had endometrial cancer.

Physical examination with speculum revealed no normal anatomy of the cervical os, which was occupied by a lesion about 6 cm in diameter with an ulcerated cauliflower-like surface and contact bleeding. It looked like cervical cancer. The mass on the cervix protruded through the entire cervical stroma into the vaginal cavity without invading the vaginal fornices or rectum. The abdomen was soft to palpation and there was no lump in the adenoids. Total body examination was unremarkable. Laboratory tests including complete blood count, liver function tests, coagulation parameters and tumor markers (including AFP, CEA, CA 125, CA 153, CA 199, CA 724, HE4, SCCA, HCG) were within reference ranges. Human papillomavirus (HPV) testing was reported as negative for a high-risk strain. Colposcopy was performed (▶ **Fig. 1** and ▶ **Fig. 2**), as was cervical biopsy and endocervical curettage. Histopathological examination combined with immunohistochemical results revealed a malignant peripheral nerve sheath tumor (MPNST). The initial microscopic differential diagnosis was cervical melanoma, but immunohistochemical analysis excluded this tumor (see Discussion). The final pathological diagnosis was malignant peripheral nerve sheath tumor, also known as malignant schwannoma.

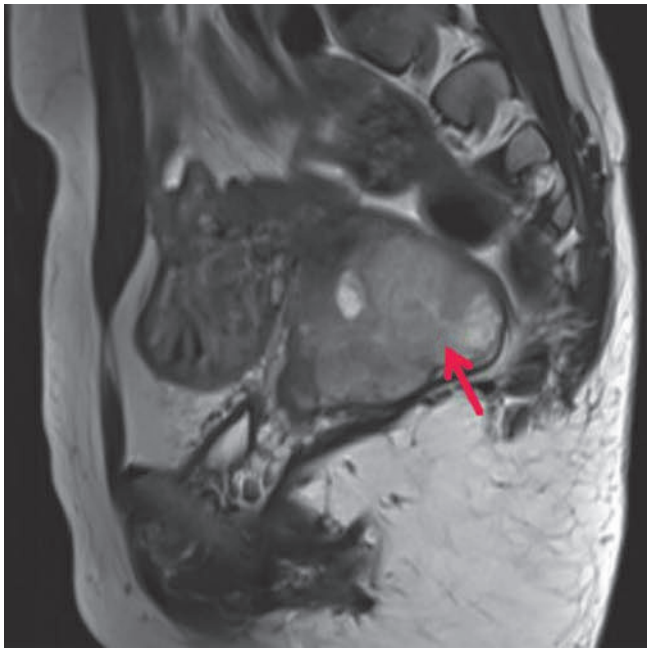
For preoperative evaluation, the patient was referred to the radiology department for pelvic magnetic resonance imaging (MRI) and abdominal computed tomography (CT). MRI showed a cervical tumor of approximately 7.0 × 5.8 × 5.4 cm invading the parametrium and upper segment of the vagina, but no invasion of the rectum. T2-weighted image sagittal scan showed no normal cervical morphology, with irregular high-signal masses and total stromal invasion of the cervix. T1-weighted image showed an



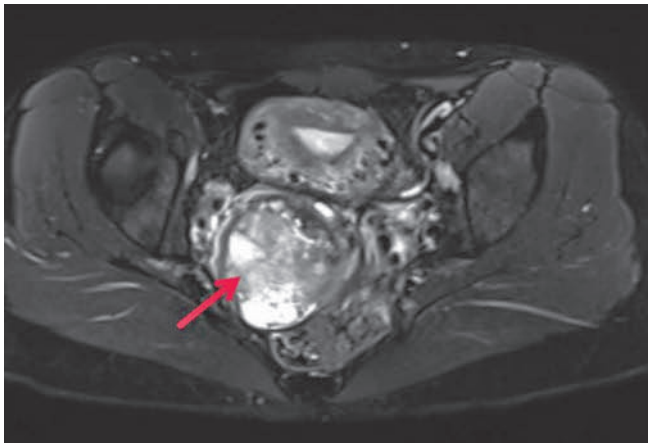
▶ **Fig. 1** No normal anatomy of the cervical os, which is occupied by a reddish-yellow lesion with a diameter of about 6 cm.



▶ **Fig. 2** On colposcopy, the tumor shows numerous atypical vessels.



▶ **Fig. 3** T2-weighted image sagittal scan showed no normal cervical morphology, with irregular high-signal masses and whole stromal invasion of the cervix.



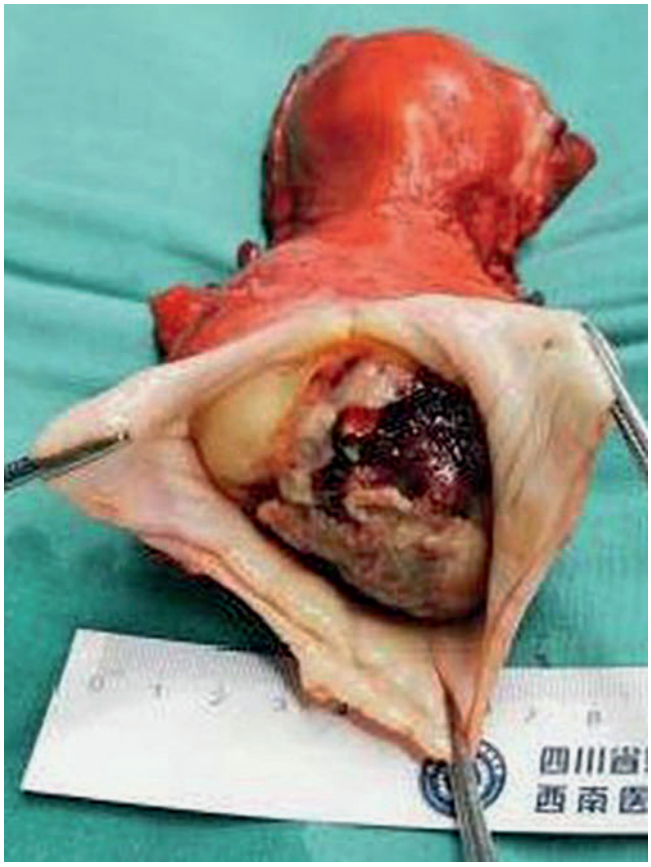
▶ **Fig. 4** Cervical irregular soft tissue mass involving the whole cervix. T1-weighted image scan showed an equal signal, and T2-weighted image and T2 lipid-suppressing sequence showed an uneven high signal, with small cystic change inside. The enhanced scan showed significantly heterogeneous enhancement.

equal signal, and the T2-weighted image and T2 lipid-suppressing sequence showed an uneven high signal, with small cystic changes within; the enhanced scan showed significantly heterogeneous enhancement (▶ **Fig. 3** and ▶ **Fig. 4**). There was no evidence of lymphadenectasis or distant metastasis on CT scan.

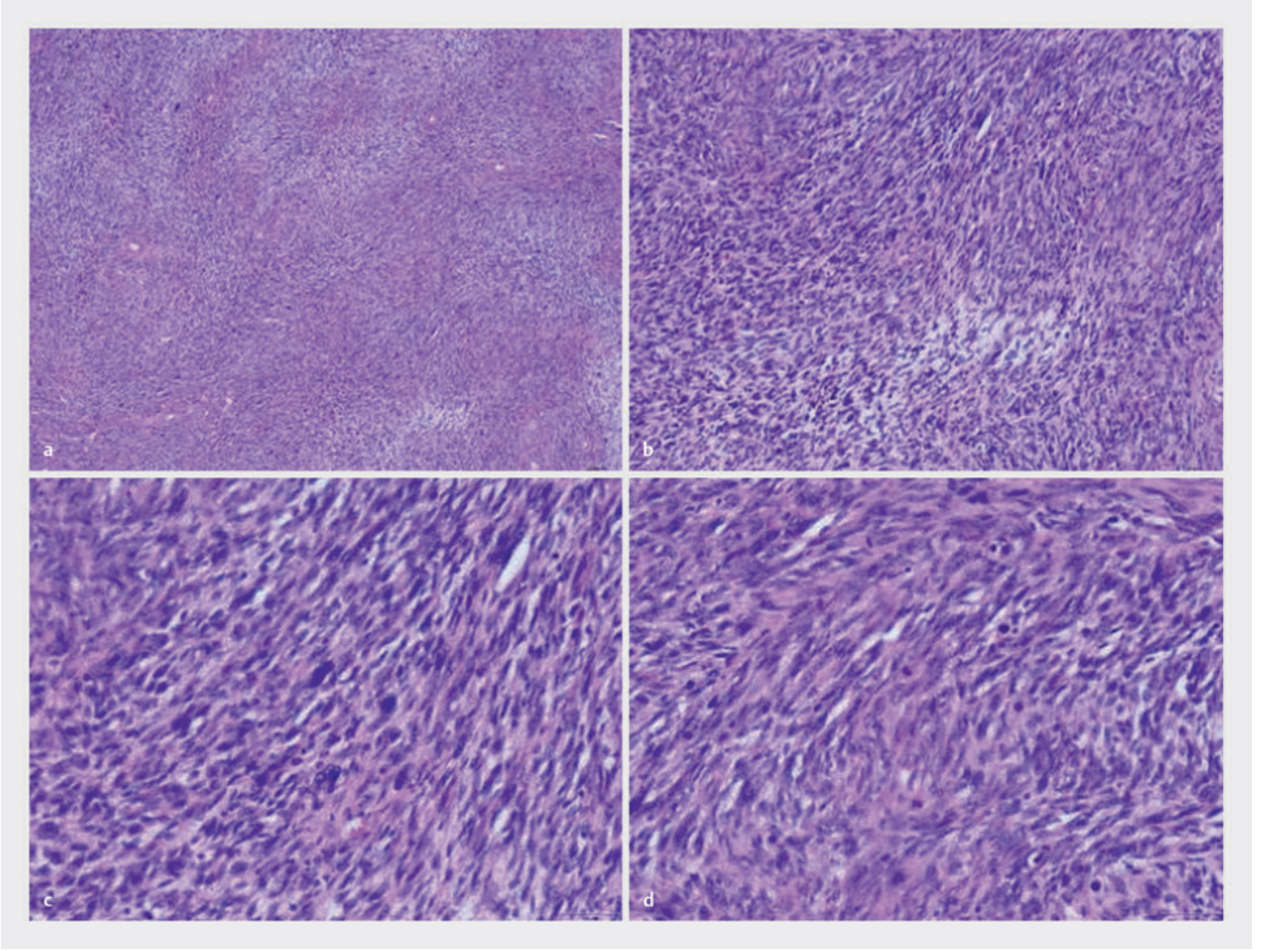
After a meeting of the MDT, we made a clinical diagnosis of cervical malignant schwannoma stage IIb, analogous to cervical cancer staging [1]. Radical resection of the tumor with wide free margins was essential to optimize the patient's prognosis, given that other therapeutic strategies (radiotherapy, chemotherapy) will not be effective against this tumor biology [2]. To achieve free margins, a wide vaginal cuff was excised. A type C hysterectomy according to the classification of Querleu & Morrow [3] was planned to preserve the bladder and ureters. The patient was prepared for surgery according to our routine preoperative procedures.

The cervical tumor was completely removed circumferentially together with the uterus and a vaginal cuff, leaving a margin of at least 2.5 cm of healthy tissue in the deep vaginal mucosa. On gross examination, the tumor had a yellowish-red appearance without necrosis, with an irregular surface measuring 6 × 4 × 3 cm (▶ **Fig. 5**). The patient's postoperative course was uneventful and there were no perioperative complications.

The case was discussed in detail at the tumor conference. It was agreed that neither radiotherapy nor chemotherapy could be considered based on the available data. Based on the sparse but still available data (see below), the patient's prognosis was not so unfavorable that experimental adjuvant therapy would be considered at this time, especially since it would have to be paid for by the patient herself. However, next-generation gene sequencing, immunotherapy and other antineoplastic options were explored in case of recurrence.



▶ **Fig. 5** Gross pathological specimen of the uterus and vaginal excision. Incised anterior vaginal wall.



▶ **Fig. 6** Photomicrograph shows a spindle cell tumor arranged in a fascicular pattern (**a** H & E 40 ×), focally myxoid stroma (**b** H & E 100 ×), some highly pleiomorphic nuclei (**c** H & E 200 ×), and atypical mitosis (**d** H & E 200 ×).

Paraffin sections and an oral mucosal swab were subjected to next-generation sequencing of 270 genes specifically selected for sarcoma at the Changke Laboratory, Beijing (https://www.ck-dx.com/).

This test revealed 5 gene mutations or gene deletions:

- HER2 mutation
- CDKN2A deletion
- CDKN2 B deletion
- TP53 mutation
- TSC2 deletion

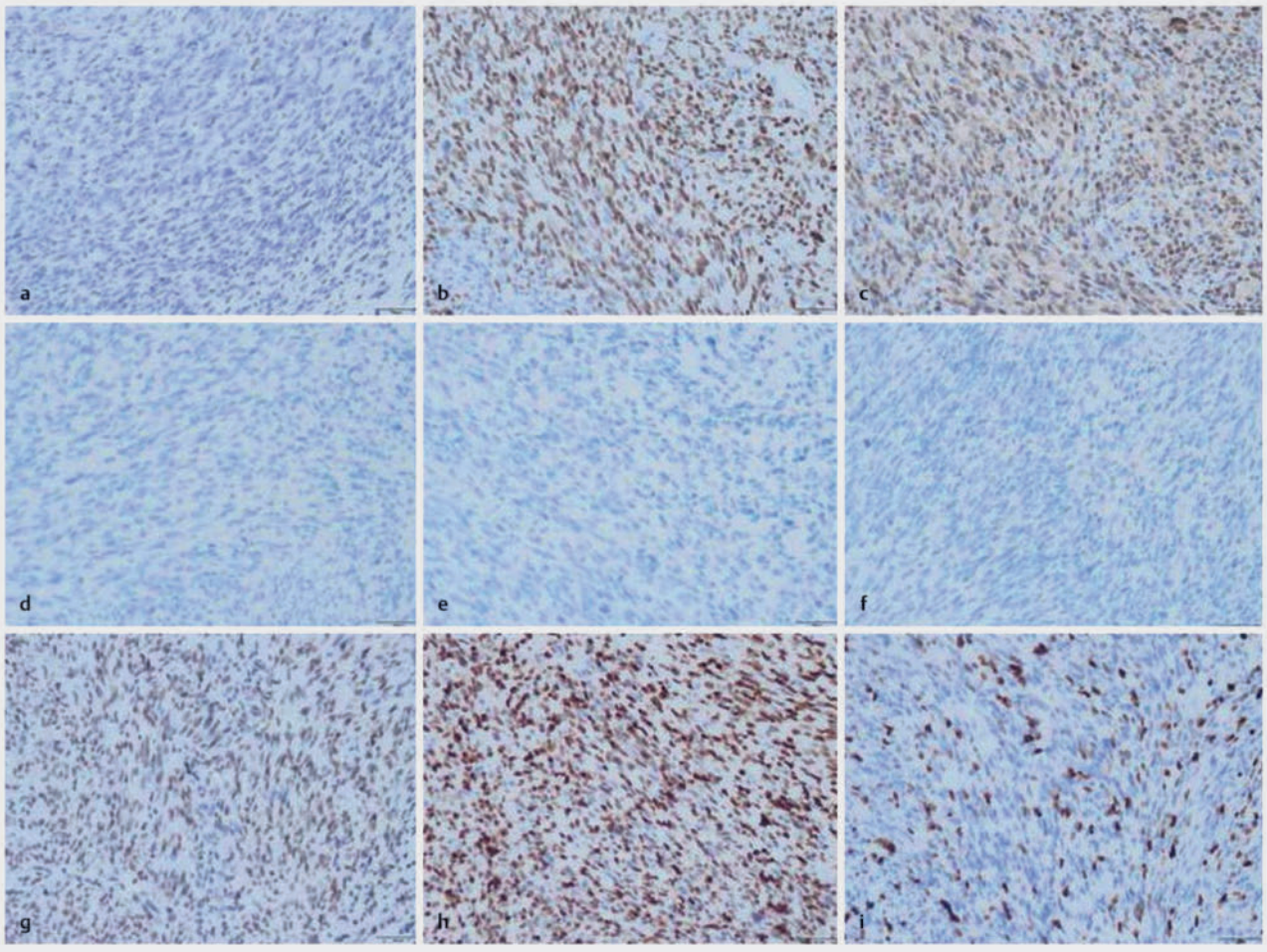
The tumor did not show microsatellite instability, mismatch repair genes were normal, and no mutations in hyperprogression-related genes were detected.

The patient presented for a first follow-up two months after surgery. All findings were unremarkable. After half a year of follow-up, the patient had pelvic and vaginal recurrence, with a palpable lump in the vaginal stump and pelvic cavity, approximately 5 cm in diameter, with an unclear border to the bladder. The biopsy showed a malignant tumor, as in the previous pathology. We discussed the treatment options and reviewed the specimens from the primary surgery. The tumor was definitively resected with at least 1.5 cm of healthy tissue on all sides. Repeat surgery without residual tumor would have meant total exenteration for the young patient, with no likelihood of a definitive cure. The patient then transferred to another university hospital and is being treated with dacarbazine 360 mg d1–5 q4w, cisplatin 40 mg d1–3 q4w and bevacizumab 400 mg d1 q4w. Response results are not yet available.

Pathological findings of the primary tumor

Macroscopically

Gross findings: The resected uterus and bilateral adnexa measured 11.8 × 10.5 × 2.7 cm. There was a large mass of 6.5 × 4.5 × 3.9 cm in the cervix from 12 o'clock to 8 o'clock and the tumor had infiltrated the outer third. There was no invasion of the corpus uteri, vaginal fornices, bilateral fallopian tubes. The vaginal margins were clear. Parametrial infiltration was confirmed. No lymphovascular invasion was present but neural invasion was.



▶ **Fig. 7** Immunohistochemical analysis of MPNST showed loss of expression of H3 K27Me3 (**a**). SOX10 (**b**) and S100 (**c**) were positive bit negative for Melan-A (**d**), HMB-45 (**e**), and Desmin (**f**). BRG1 (**g**) was not absent. Mutant P53 (**h**) expression, and elevated Ki67 (**i**) labeling are also features of MPNST.

There were no lymphatic metastases. The tumor was categorized as pTN stage pT2 bN0 according to cervical cancer classification.

Microscopic

Microscopic examination revealed densely cellular compact bundles of spindle cells arranged in a fascicular pattern with perivascular condensation and focally myxoid stroma. The nuclei were elongated with tapered ends and there was little eosinophilic cytoplasm, with highly atypical hyperchromatic nuclei and sparse cytoplasm. Mitosis was active at a rate of 5–8 per high-power field (▶ **Fig. 6**).

Immunohistochemistry

Immunohistochemical staining showed that tumor cells were positive for S-100 and SOX10, with the majority of tumor areas showing loss of H3 lysine 27 trimethylation (H3 K27Me3) and mutant P53 expression. The cells were negative for Desmin, SMA, HMB-45, Melan-A, CD10. The expression of BRG1 and INI-1 was positive with a Ki67 labeling index of approximately 30 % (▶ **Fig. 7**).

Differential diagnosis

The differential diagnosis of large cervical masses includes endometrioid stromal sarcoma, leiomyosarcoma, and especially spindle cell melanoma. Melanoma can be excluded in cases without expression of HMB-45 and Melan-A. Lack of expression of supportive stromal and myogenic cell markers (i.e., Desmin, SMA, CD10) excluded endometrioid stromal sarcoma and leiomyosarcoma. Tumor-positive expression of Schwann cell markers (i.e., S-100 and SOX10) and loss of H3 K27me3 expression, a highly specific marker for MPNST, were included in the diagnosis.

Discussion

In addition to the hereditary form of nerve tumors (neurofibromatosis type 1 [NF1]), there are solitary nerve tumors, often referred to as schwannomas or Schwann cell tumors. Most Schwann cell

tumors are benign and only a rare minority have malignant criteria. When a tumor is found around a peripheral nerve or within the brachial or pelvic plexus, the diagnosis is obvious and only differentiation between malignancy and non-malignancy is required. Even under benign conditions, complete removal of the tumor may be difficult.

Malignant peripheral nerve sheath tumors (MPNSTs) are malignancies that arise from the cells that sheath the nerve fibers of peripheral nerves (Schwann cells) [4]. They infiltrate peripheral nerves and account for approximately 10 % of soft tissue malignancies. The estimated incidence of MPNST is 1.46 per 1 000 000 [5]. They develop in approximately 8–13 % of people with neurofibromatosis type 1. Neurofibromatosis type 1 (NF1) is an inherited disorder. MPNSTs are associated with a poor prognosis and are the leading cause of death in NF1 patients [2]. The 8–13 % of individuals with NF1 mutations who develop MPNSTs account for nearly 50 % of all MPNST cases. Of the remaining cases, 45 % of MPNSTs occur sporadically with unidentified genetic abnormalities and the remainder are associated with radiation therapy. MPNST are most common in adults aged 30–60 years, with a median age of 37 years and an age range of 7–94 years. Children and adolescents are also at risk of developing MPNST, but it is relatively rare [6], about 13 %, and less common in children under six years of age, although slightly more common in males. MPNSTs occur primarily in the trunk, the proximal extremities, and neck [7]. The occurrence of most tumors is closely associated with the peripheral nerve trunks (e.g. sciatic, sacral and brachial plexus). Therefore, these tumors are most commonly found in the buttocks, thighs, upper arm and the paraspinal area, but rarely in the head and neck (mostly in the trigeminal and auditory nerves). In organ structures, MPNSTs are rare and the differential diagnosis is difficult. In the past, misdiagnosis was possible without immunohistochemistry. Clinically, MPNSTs may be associated with pain, especially in patients with NF 1, and are usually located in deep soft tissues, with occasional superficial involvement [8].

Nowadays the diagnosis of malignant peripheral schwannoma is based on histomorphological and finally immunohistochemical diagnosis. The main microscopic differential diagnosis is melanoma. Melanoma can be excluded in cases without expression of HMB-45 and Melan-A. Positive expression of Schwann cell markers (i.e., S-100 and SOX10) and loss of H3 K27me3 expression, which is a highly specific marker for MPNST, make the diagnosis certain. The histologic cell types of malignant schwannomas include glandular, melanocytic, malignant triton and epithelioid types [9]. 50–70 % of tumors express S-100 at variable levels and, in general, the higher the malignancy, the lower the expression of S-100. In addition to S-100, they may also express SOX10 at variable levels and occasionally express focal CK8 and CK18, but without expression of CK7 and CK19 [10].

It is possible that Sloan [11] reported the first case of a schwannoma in 1988, which was described as a melanocytic schwannoma and did not include determination of HMB-45, so that the differential diagnosis between melanoma and schwannoma is uncertain from today's perspective. This patient was still free of recurrence after 10 years. The publication by Junge et al. dates from 1989 [12] and the authors are believed to be the first to report a malignant schwannoma. They reported on a 45-year-old patient who also underwent hysterectomy with pelvic lymphadenectomy. The histopathological examination described the typical picture of a malignant schwannoma (MPNST). The tumor was S-100 and vimetin positive, but Desmin and cytokeratin negative. No follow-up information is available.

Bernstein et al. [13] published a case of epithelioid malignant schwannoma of the cervix uteri in 1999. The patient was a 65-year-old Caucasian woman. She underwent radical hysterectomy with bilateral adnexectomy and pelvic and para-aortic lymphadenectomy. The tumor was histomorphologically negative for the melanoma-associated antigen HMB-45 and strongly positive for S-100 antigen. They compared their case with the publication by Junge et al., which was a spindle cell schwannoma (S-100 positive), and with the publication by Terzakis et al. [14], which was classified as a melanocytic schwannoma (S-100 positive, HMB-45 positive, keratin negative, GFAP negative). In the latter case, the diagnosis of schwannoma is questionable because of the HMB-45 positivity.

Later publications [15] (with three cases), [16, 17, 18] followed. Kim et al. [19] treated a 50-year-old woman with this condition. She underwent hysterectomy and bilateral salpingo-oophorectomy (BSO). Lymph node dissection was also performed. The patient received chemotherapy with cyclophosphamide and cisplatin. Despite this intensive primary therapy, the patient relapsed after six months. This case showed an atypical immunohistochemistry, the marker HBM-45 was positive. They compared this case with a single other MPNST case with positive HBM-45, a malignant schwannoma of the skin [20].

Mills et al. [21] reported three cases of malignant schwannoma. The patients were aged 25, 32 and 60 years. The 32-year-old man was free of recurrence for 33 months after tracheal resection and brachytherapy. The 60-year-old woman underwent hysterectomy. She had a recurrence at 30 months. A 25-year-old woman underwent local excision only. This patient developed a recurrence after six months and died rapidly. In the 53-year-old patient reported by Akhavan et al. [22], complete resection of the malignant schwannoma was not possible. The patient received radiochemotherapy, which did not result in tumor control.

Dong et al. [23] reported mainly on CT and PET/CT imaging in a 45-year-old female patient. The imaging is almost identical to the case reported here. The patient underwent laparoscopic radical hysterectomy with bilateral adnexectomy and lymph node dissection. No information is available on the patient's outcome in this primarily image-guided procedure. Sangiorgio et al. [25] reported the case of a 45-year-old woman with an MPNST of the cervix uteri. They point out that the differential diagnosis of melanoma, leiomyosarcoma, endometrial stromal sarcoma, synovial sarcoma and other spindle cell neoplasms must be carefully considered.

Zhang et al. [25] reported on a 46-year-old woman who was diagnosed after radical hysterectomy with the final specimen investigated by histology and immunohistochemistry. One year later, the patient relapsed and developed pulmonary metastases. She received combination chemotherapy with epirubicin/ifosfamide, dacarbazine and etoposide/cisplatin. Median survival was 44 months. In a very recent paper, Nair et al. [26] reported a case

in which preoperative radiotherapy was followed by radical hysterectomy with bilateral adnexectomy.

When the 18 confirmed cases of MPNST, including our case, are combined, the prognosis is unfavorable (▶**Table 1**). Of the 12 cases that could be followed, six had recurrence or primary progression. Six cases have survived (50%). In some cases, follow-up is too short to make a definitive assessment. The mortality rate is also very high, at least 50%. Primary surgery with secure tumor-free margins is required. Whether hysterectomy or even radical hysterectomy is necessary to achieve this cannot be definitively assessed in these cases. In any case, accurate imaging with MRI should be performed to prove or exclude parametrial invasion. Our case shows that the preoperative imaging suggested a parametrial lesion, which was then confirmed on the surgical specimen. The case of Rodriguez et al. [18], a 22-year-old woman who remained free of recurrence after trachelectomy, shows that organ-sparing resection must be discussed on a case-by-case basis and may be justified in women who wish to have children. Our case confirms that even resection far into healthy tissue is no guarantee that local recurrence will not occur.

Lymph node metastases are not described in any of the studies, and even in our own case the pelvic and para-aortic lymph nodes were tumor-free despite the diagnosis of parametrial involvement. The question of lymphadenectomy should also be decided on a case-by-case basis but may be unnecessary.

Data from MPNSTs of other localizations also show that the tumor is not sensitive to either radiotherapy or chemotherapy. The prognosis for malignant schwannomas is poor. Surgery is the first line of treatment and complete excision with free margins is essential [2].

The most important prognostic factors in MPNST were the presence of neurofibromatosis, tumor size > 5 cm, and extent of

▶**Table 1** Published cases of MSRNT.

No	Author	Year	Age at diagnosis	Subtype	Therapy	Follow-up	IHC
1	Sloan [11]	1988	47	Melanocytic schwannoma	Hysterectomy and BSO	Tumor free at 10 years	S-100 pos
2	Junge et al. [12]	1989	45	Spindle cell schwannoma	Hysterectomy and pelvic lymphadenectomy	No data	S100 pos Vimentin pos Desmin neg Cytokeratin neg
3?	Terzakis et al. [14]	1990	47	Melanocytic schwannoma	No data	No data	S-100 pos HMB-45 pos
4	Lallas et al. [16]	1997	52		Hysterectomy and BSO	Tumor free at 10 years	S-100 neg Vimentin pos
5	Keel et al. [15]	1998	25		Cone resection and hysterectomy	Too short	S-100 pos Vimentin pos Cytokeratin neg Desmin neg HMB-45 neg
6			65		Hysterectomy	Too short	S-100 pos Vimentin pos Cytokeratin neg HMB-45 neg
7			73		Hysterectomy and pelvic lymphadenectomy	Metastasis after 20 months	S-100 pos Vimentin pos Cytokeratin neg HMB-45 neg
8	Bernstein et al. [13]	1999	65		Radical hysterectomy and BSO & pelvic and para-aortic lymphadenectomy	No data	S-100 pos HMB-45 neg Cytokeratin neg
9	Di Giovannantonio et al. [17]	2005	27		No data	Disease free at 34 months	S-100 pos Vimentin pos Keratin neg Desmin neg Actin neg HMB-45 neg
10	Rodriguez et al. [18]	2006	22		Trachelectomy	Disease free at 20 months	S-100 pos HMB-45 neg CD-10 neg

▶Table 1 continued

No	Author	Year	Age at diagnosis	Subtype	Therapy	Follow-up	IHC
11?	Kim et al. [19]	2009	50		Radical hysterectomy and BSO and lymphadenectomy Chemotherapy (cyclophosphamide and cisplatin 6 cycles)	Progression after 6 months	S-100 pos HMB-45 pos Melan-A neg Desmin neg SMA neg NSE neg
12	Mills et al. [21]	2011	32		Trachelectomy and brachytherapy	Disease free at 33 months	S-100 pos CD-34 pos Vimentin pos Glial fibrillary acid neg NF-1 neg SOX-10 neg EMA neg CD-56 neg HMB-45 neg
13			60	Associated with other nerve sheath tumors	Hysterectomy	Local recurrence after 13 months	S-100 pos CD-34 pos Vimentin pos Glial fibrillary acid neg NF-1 neg SOX-10 neg EMA neg CD-56 neg HMB-45 neg
14			25		Local excision	Tumor recurrence after 6 months and rapid death	S-100 pos CD-34 pos Vimentin pos Glial fibrillary acid neg NF-1 neg SOX-10 neg EMA neg CD-56 neg HMB-45 neg
15	Akhavan et al. [22]	2012	53		Surgery impossible Radiochemotherapy	Progression	S-100 pos Vimentin pos Desmin focally pos Cytokeratin neg HMB-45 neg
16	Dong et al. [23]	2014	45		Laparoscopic radical hysterectomy & BSO & pelvic lymphadenectomy	No data	S-100 pos KI-67 40%
17	Sangiorgio et al. [25]	2018	45		Radical hysterectomy	Tumor free at 12 months	S-100 pos HMB-45 neg p16 neg CD10 neg E2 neg SOX10 neg GFAP neg CD56 neg Cytokeratin neg AE1/AE3 neg Desmin neg h-Caldesmon neg SMA neg ALK neg EMA neg Bcl2 neg CD99 neg

▶**Table 1** continued

No	Author	Year	Age at diagnosis	Subtype	Therapy	Follow-up	IHC
18	Zhang et al. [25]	2022	46		Radical hysterectomy	Died after 44 months	?
19	Nair et al. [26]	2023	44		Radical hysterectomy and BSO	Too short	S-100 pos HMB-45 neg Melan-A neg
20	Present case	2023	29		Radical hysterectomy and BSO and pelvic lymphadenectomy	Local recurrence after half a year	

2 cases uncertain due to HMB-45 positivity
Remaining 18 cases
- Lost to follow-up: 3 cases
- Too short for follow-up: 3 cases
- Cases with follow-up: 12 cases

- Recurrence free: 6 cases (50%)
- Recurrence: 6 cases (50%)

resection. Complete resection improved survival, but adjuvant radiation or chemotherapy did not. Five- and ten-year overall survival rates were 34% and 22%, respectively [29, 28]. In sporadic MPNST, the radicality of the resection with tumor-free margins seems to be the only prognostic factor. Perhaps the localization of the tumor in the cervix uteri also favors prognosis, as the disease can be detected relatively early on and is easily accessible for radical resection. The patient in our case apparently had no signs of neurofibromatosis (no café-au-lait plaques or neurofibromas) and must be classified as a sporadic malignancy. Of the 18 confirmed cases of cervical schwannoma seen today, only one patient had evidence of neurofibromatosis. All other patients appeared to be sporadically affected.

The next-generation sequencing results were interpreted in two ways. First, they were used to perform a differentiated genetic analysis of the tumor, as this had not been done in any of the other case reports. The second use was to determine possible therapeutic approaches in the event of recurrence, as it is known that recurrence can occur at a very early stage.

The protein encoded by the TSC2 gene is a tumor suppressor in the mTOR signaling pathway that is inactivated by mutations or deletions in a variety of cancers. TSC2 is a key negative regulator of the proto-oncogenic mTOR pathway [29]. The mTOR signaling pathway plays an important role in promoting cell growth and regulating protein synthesis. Somatic mutations in TSC2 have been found in several cancers, including liver cancer and endometrial cancer, and are mainly truncated loss-of-function mutations. Loss-of-function mutations of TSC2 cause constitutive activation of the mTORC1 complex, leading to the opposite effect of mTOR inhibitors. The FDA has approved everolimus for the treatment of CNS cancers with mutations in the TSC2 gene. Clinical trials of targeted drugs for solid tumors with the TSC2 gene mutation are underway abroad, and the test drugs are sapanisertib and samotolisib. On this basis, everolimus would be a current treatment option.

In carcinomas, CDKN2A is altered by mutation and/or deletion. The CDKN2A gene encodes two unique proteins, p16 (Ink4a) and p14 (ARF), which are important in regulating cell cycle progression [30]. The p16 (Ink4a) is a cyclin-dependent kinase (CDK) inhibitor that represses CDK 4 and CDK 6 by preventing CDK 4 and CDK 6 from binding to cyclin. Loss of CDKN2A in the mouse model leads to spontaneous carcinogenesis, consistent with its role as a tumor suppressor [31]. To date, no targeted drugs based on the CDKN2A deletion mutation have been approved for this type of cancer.

If ERBB2 (HER2) (p.Val777Leu) mutation is detected, FDA approval and NCCN guidelines recommend using trastuzumab and other drugs to treat NSCLC with this gene mutation [32]. Whether cross-cancer drugs should be chosen must be determined by clinicians.

As a result of gene sequencing, the mTOR inhibitor everolimus would initially be administered as an off-label use in the event of a relapse. Another treatment option is the use of trastuzumab, which is also off-label. The colleagues at the other hospital did not base their treatment protocol on the gene sequencing done with their results. We had an NGS result in this patient that showed us a possible benefit of two drugs, trastuzumab and everolimus, and we did not have the opportunity to use and test these drugs because the patient changed hospital, which is unfortunate.

Conclusion

Although the cervix is a rare site for schwannoma, it should be considered in the differential diagnosis of any obscure cervical mass. Due to their rarity, the diagnosis of these tumors remains a challenge for both clinicians and pathologists. Currently, complete surgical resection is the mainstay of treatment, and the goal of radicality should always guide the decision-making process. However, even complete resection far into healthy tissue does not guarantee a cure.

Conflict of Interest

The authors declare that they have no conflict of interest.

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