Malignant peripheral nerve sheath tumor of the uterine cervix: A case report and literature review

XUENI LIU and LEI LI

Department of Pathology, West China Second University Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan 610041, P.R. China

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Abstract. Malignant peripheral nerve sheath tumors (MPNSTs) are rare high-grade sarcomas arising from the peripheral nerves or peripheral nerve sheath cells. MPNSTs rarely occur in the soft tissue, especially in the uterine cervix. Few cases of cervical MPNST have been reported in the literature. The present study reports the case of a 36-year-old female patient who presented with vaginal bleeding. A cervical mass was detected by vaginal ultrasonography and the patient was diagnosed with MPNST via assessment of the morphological and immunohistochemical features of the tumor after surgery. The patient received chemotherapy and radiotherapy following surgery, and at 8 months post-treatment, had no recurrence or metastasis. Furthermore, the present study summarizes the characteristics of all reported cases of cervical MPNST and their potential differential diagnosis with other spindle cell tumors.

Introduction

Cervical cancer is a common malignancy of the female reproductive system and poses a serious threat to the lives and health of middle-aged and elderly women. The global age-standardized incidence of cervical cancer is 13.3 per 100,000 women-years and the mortality rate is 7.2 per 100,000 women-years (1). Squamous cell carcinoma is the main type of cervical cancer, accounting for ~80% of cases, with adenocarcinoma and adenosquamous carcinoma accounting for ~15% of cases and other malignant tumors accounting for ~5% of cases, among which sarcoma accounts for <1% of cases (2). Malignant peripheral nerve sheath tumors (MPNSTs), also known as malignant neurilemomas, malignant schwannomas, neurofibrosarcomas or neurogenic sarcomas, show differentiation toward peripheral nerve sheath cells. The major nerve trunks, including the sciatic nerve, brachial plexus and sacral plexus, are usually the development sites, and the tumors are associated with neurofibromatosis-1 (NF-1) in ~50% of cases (3). Studies have reported that MPNSTs account for only ~3% of cervical sarcomas (4), making it a rare cervical malignancy.

The present report describes a case of MPNST of the uterine cervix and discusses the morphological and immunohistochemical characteristics, and the possible differential diagnosis of MPNST and other spindle cell neoplasms.

Case report

A 36-year-old female attended the West China Second University Hospital, Sichuan University (Chengdu, China) in December 2022 after having a small amount of vaginal bleeding for 10 days following sexual intercourse. Vaginal ultrasonography in another hospital immediately prior to admission showed a cystic mass in the cervical segment measuring ~5.8x4.8x5.3 cm (Fig. 1). Thinprep cytological tests and human papillomavirus assessments showed no abnormalities. The patient had no personal history of neurofibroma or a family history of cervical cancer.

After completing all preoperative examinations, such as computed tomography imaging and relevant blood tests, the patient underwent a total abdominal hysterectomy and bilateral salpingectomy, as well as a pelvic lymph node dissection when malignancy was suspected during surgery. The mass was observed in the external cervical os and the cervical canal, with a size of ~4x3.5x2 cm, and the mass section was grayish-yellow. Bleeding and necrosis could be seen in certain areas, infiltrating the whole layer of the cervical interstitium and part of the uterine muscle wall, and the mass was found to involve the vaginal vault and vaginal wall (Fig. 2). The endometrium was slightly thickened and there was no obvious mass in the bilateral adnexa. Extensive sampling and sectioning of the cervical mass, myometrium and endometrium were performed for histopathological examination. The tissue was fixed with 4% neutral formalin (for 24 h at 25˚C) and embedded in paraffin, and then 4-μm sections were prepared

Correspondence to: Professor Lei Li, Department of Pathology, West China Second University Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, 20 Renmin Road South, Chengdu, Sichuan 610041, P.R. China
E-mail: lipath@163.com

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that were subjected to hematoxylin and eosin (H&E) staining (for 8 h at 25˚C).

Microscopically (Olympus BX43), the tumor was composed mainly of tightly packed spindle cells with dense cell proliferation. The cell boundaries were not clear and the tumor was arranged in a cross bundle. The tumor showed invasive growth, invading the whole layer of the cervical interstitium, the vaginal fornix and its disjunction, and the uterine muscle wall. The cytoplasm was sparse, the nuclei were oval, elongated and moderately atypical, and some cells had small eosinophilic nucleoli. Mitotic activity was high, with ≤30 mitoses per 10 high-power field, and bleeding and necrosis were also observed. The tumor did not destroy the squamous epithelium, endocervical glands or endometrial glands (Fig. 3). In addition, myxoid and edematous areas of low cell density were also observed, alternating with areas of dense cells. No tumor was found in the vaginal stump, bilateral parametrial tissues, bilateral pelvic lateral wall surgical margins or bilateral fallopian tubes. All negative margins were >3 cm away from the tumor.

Section preparation for immunohistochemical staining was the same as that for H&E staining. All immunohistochemical staining was performed with an automated staining system Bond III (Leica Biosystems Newcastle Ltd.) based on the EnVision method. All primary antibodies with working liquid were from Fuzhou Maixin Biotech Co., Ltd., and were incubated with the sections for 15 min at room temperature. The BOND polymer Refine Detection kit (cat. no. DS9800) from Leica Biosystems, using Bond III, including 3-4% hydrogen peroxide as the peroxide block, was used for 5 min at room temperature, and then anti-rabbit poly-HRP IgG (<25 μg/ml; from DS9800 kit) was incubated with the sections for 8 min at room temperature. All immunohistochemical staining was observed using an Olympus BX43 microscope. The neoplastic cells were strongly and diffusely immunoreactive for vimentin (cat. no. MAB-0735), S-100 (cat. no. Kit-0007), sex determining region Y-box 10 (SOX-10; cat. no. RMA-1058), CD56 (cat. no. MAB-0743), protein gene product 9.5 (PGP9.5; cat. no. RAB-0076), p53 (cat. no. MAB-0674), brahma-related gene 1 (BRG-1; cat. no. RMA-1063), integrase interactor 1 (INI-1; cat. no. MAB-0696), friend leukemia virus integration 1 (FLI-1; cat. no. MAB-0649) and CD99 (cat. no. MAB-1012), with focal reactivity for CD57 (cat. no. MAB-0257), smooth muscle actin (SMA; cat. no. MAB-0890), calponin (cat. no. MAB-0712), cyclin D1 (cat. no. RMA-0541) and anaplastic lymphoma kinase (ALK, cat. no. RMA-1032) (all ready-to-use). The tumor cells were negative for human melanoma black 45 (HMB-45; cat. no. MAB-0098), melanoma antigen (Melan-A; cat. no. MAB-0275), glial fibrillary acidic protein (GFAP; cat. no. MAB-0769), epidermal growth factor receptor (EGFR; cat. no. RMA-0804), signal transducer and activator of transcription 6 (STAT6; cat. no. RMA-0845), epithelial membrane antigen (EMA; cat. no. Kit-0011), cytokeratin-pan (CK-pan; cat. no. RAB-0050), desmin (cat. no. MAB-0766), caldesmon (cat. no. MAB-0643), CD10 (cat. no. MAB-0668), B-cell lymphoma 6-corepressor (BCOR; cat. no. MAB-0879), myogenin (cat. no. MAB-0866), myoblast determination protein 1 (MyoD1; cat. no. MAB-0822), estrogen receptor (ER; cat. no. Kit-0012), progesterone receptor (PR; cat. no. Kit-0013), CD34 (cat. no. Kit-0004), CD31 (cat. no. MAB-0720) and tyrosine receptor kinase (TRK; cat. no. RMA-1072) (all ready-to-use). The Ki67 (cat. no. MAB-0672; ready-to-use) proliferation index was the proportion of positive tumor cells counted, and the average of the four high-power fields was calculated from the selected hot spot. Due to the uneven distribution of positive tumor cells, the Ki67 proliferation index was 20-50%. All immunohistochemical results are shown in Figs. 4-7.

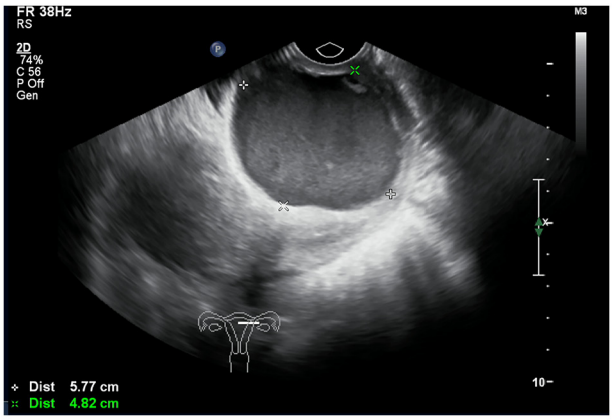

Figure 1. Representative vaginal ultrasonography image.

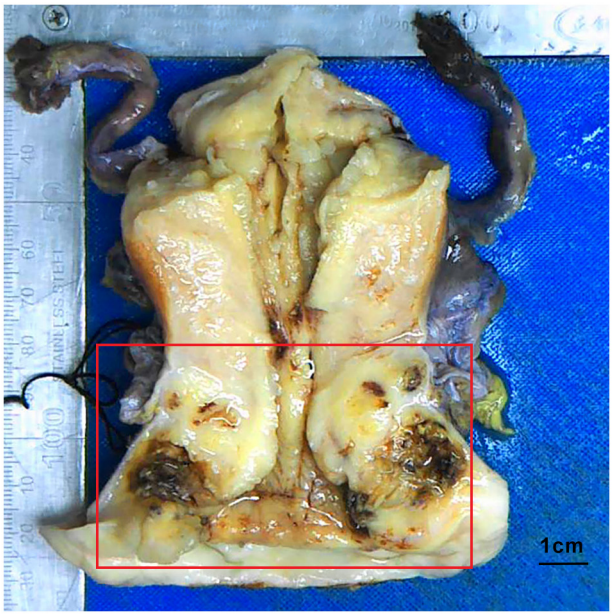

Figure 2. Location and section of cervical mass as indicated by the red box.

Based on the results of histomorphology and immunohistochemistry, the patient was diagnosed with MPNST after a review by two senior pathologists. After that, next-generation sequencing (NGS) was performed by Precision Scientific (Beijing) Co., Ltd. All gene exons were detected for the DNA of germ lines and tumor tissues (the tumor cell content should be >10%), and the NGS was performed using the NovaSeq 6000 Sequencing System (Illumina Inc.) with the Oncobuster kit (Precision Scientific, Ltd.). The results showed that no pathogenic or potentially pathogenic germline mutations were present in the patient. The only somatic mutations detected

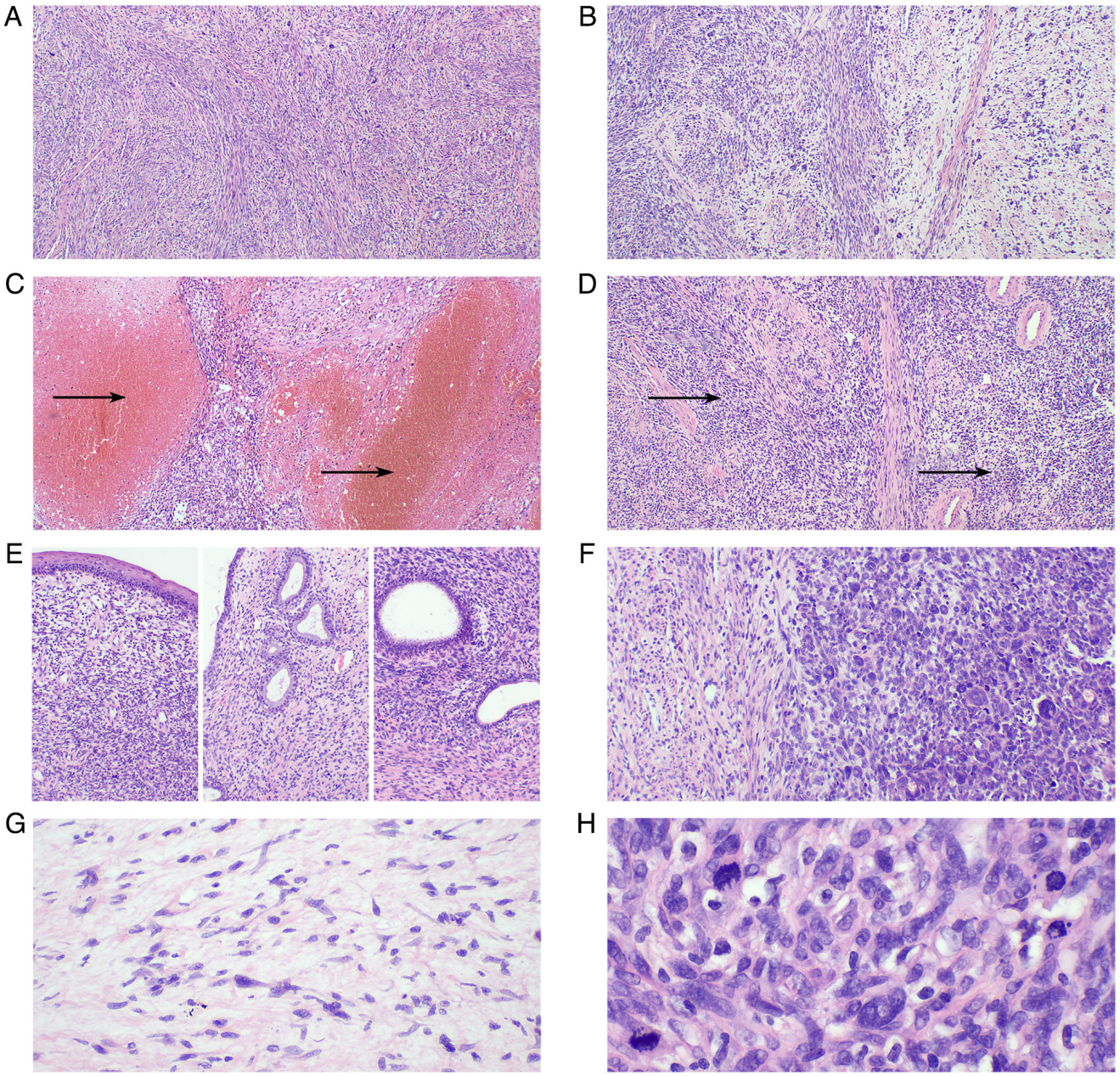

Figure 3. Morphological characteristics of the cervical malignant peripheral nerve sheath tumor. (A) The tumor was composed mainly of spindle cells (magnification, x40). (B) Certain areas exhibited obvious cell density and loose areas (magnification, x40). (C) Bleeding and necrosis were present in certain areas, as indicated by the arrows (magnification, x40). (D) The tumor contained a number of thick-walled blood vessels and the tumor cells formed a plexiform structure around the blood vessels, as indicated by the arrows (magnification, x40). (E) The tumor did not involve the squamous epithelium, endocervical glands or endometrial glands (magnification, x100). (F) The tumor cells in some areas were epithelioid, with numerous multinuclear giant cells observed (magnification, x100). (G) Comma-like Schwann cells can be seen in the loose area of cells (magnification, x200). (H) Numerous mitotic figures can be seen at a high magnification (magnification, x400).

with potential clinical significance were those in tumor protein 53 (c.422G>A p.C141Y) and erb-B2 receptor tyrosine kinase 2 (c.2329G>T p.V777L). The molecular changes in this case were not specific to MPNST or typical of it, which made the clinical follow-up treatment difficult. The patient received one dose of ifosfamide (IFO; 1.5 g ivgtt, days 1-3) + etoposide (VP16; 120 mg ivgtt, days 1-3) chemotherapy, followed by 12 radiotherapy sessions and then cisplatin (DDP; 40 mg ivgtt, days 1-3) concurrent chemotherapy. At 8 months post-surgery, the general condition of the patient was good. Positron emission tomography-computed tomography was performed at 3-month intervals, with no tumor recurrence or metastasis detected.

Discussion

MPNSTs rarely occur in the soft tissue, especially in the uterine cervix. These tumors are more common in middle-aged women presenting with abnormal vaginal bleeding and have a poor prognosis due to the highly aggressive nature of the tumors. Currently, only 17 cases of cervical MPNSTs have been reported in the literature (2,5-16), and

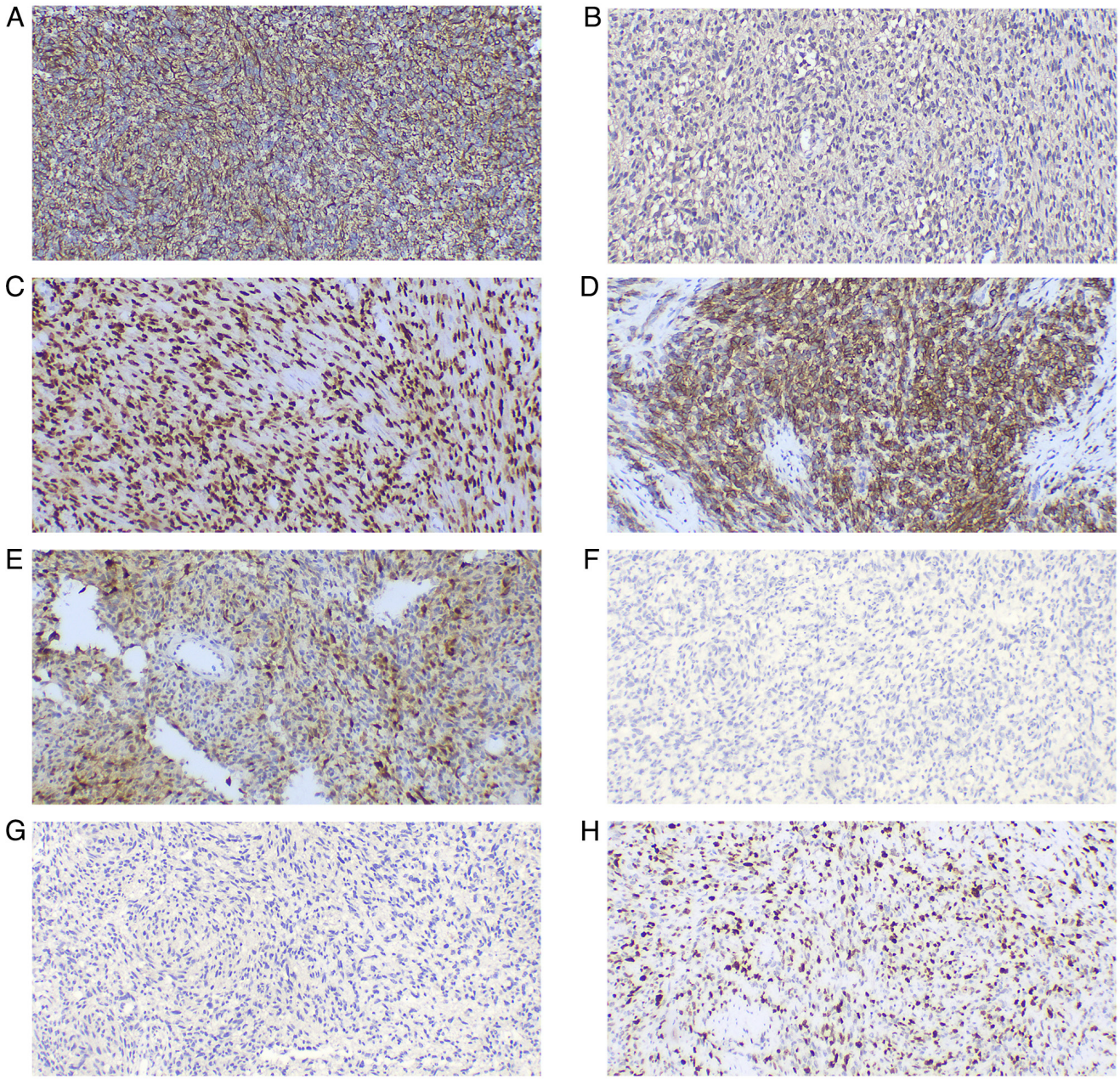

Figure 4. Immunohistochemical characteristics of the cervical malignant peripheral nerve sheath tumor. (A) Vimentin^{+}, (B) S-100^{+}, (C) sex determining region Y-box 10^{+}, (D) CD56^{+} and (E) protein gene product 9.5^{+} staining. (F) Human melanoma black 45- and (G) desmin^{-} staining. (H) The Ki67 index was 20-50%. Magnification, x100.

the clinicopathological characteristics of these cervical MPNSTs are presented in Table I, together with those of the current case.

The reported age of cervical patients with MPNST ranges from 21-73 years, with a median age of 47 years and a mean age of 45.3 years. The patient in the present report was 36 years old. The clinical manifestation in these patients is abnormal vaginal bleeding. Furthermore, it has been reported that 40-50% of patients with MPNST have NF-1, which has been associated with a more aggressive disease (3,17,18). The first symptom of the patient in the present case was vaginal bleeding and the patient had no history of NF-1. MPNSTs can easily metastasize to the lungs, but regional lymph node metastasis is rare (17-19). As a result of early detection, lymph node metastasis and distal organ metastasis did not occur in the patient in the present study.

Cervical MPNST is similar to neoplasms of the same type occurring in other soft tissues. The neoplasms measure 3-4 cm and are generally polypoid or cervical canal masses that may invade the cervical interstitium but do not destroy the endocervical glands (7). The tumor is composed of tightly packed atypical spindle cells with high mitotic activity, and its growth pattern is similar to that of fibrosarcoma, arranged in herringbone, storiform or nodular patterns (5-8). The tumor cells exhibit diffuse growth and can form alternating distributions of rich and sparse areas of cells. Dense tumor cells are commonly found around blood vessels in mucoid areas, which is called the plexiform pattern. At high magnification, the tumor cells show the morphological characteristics of

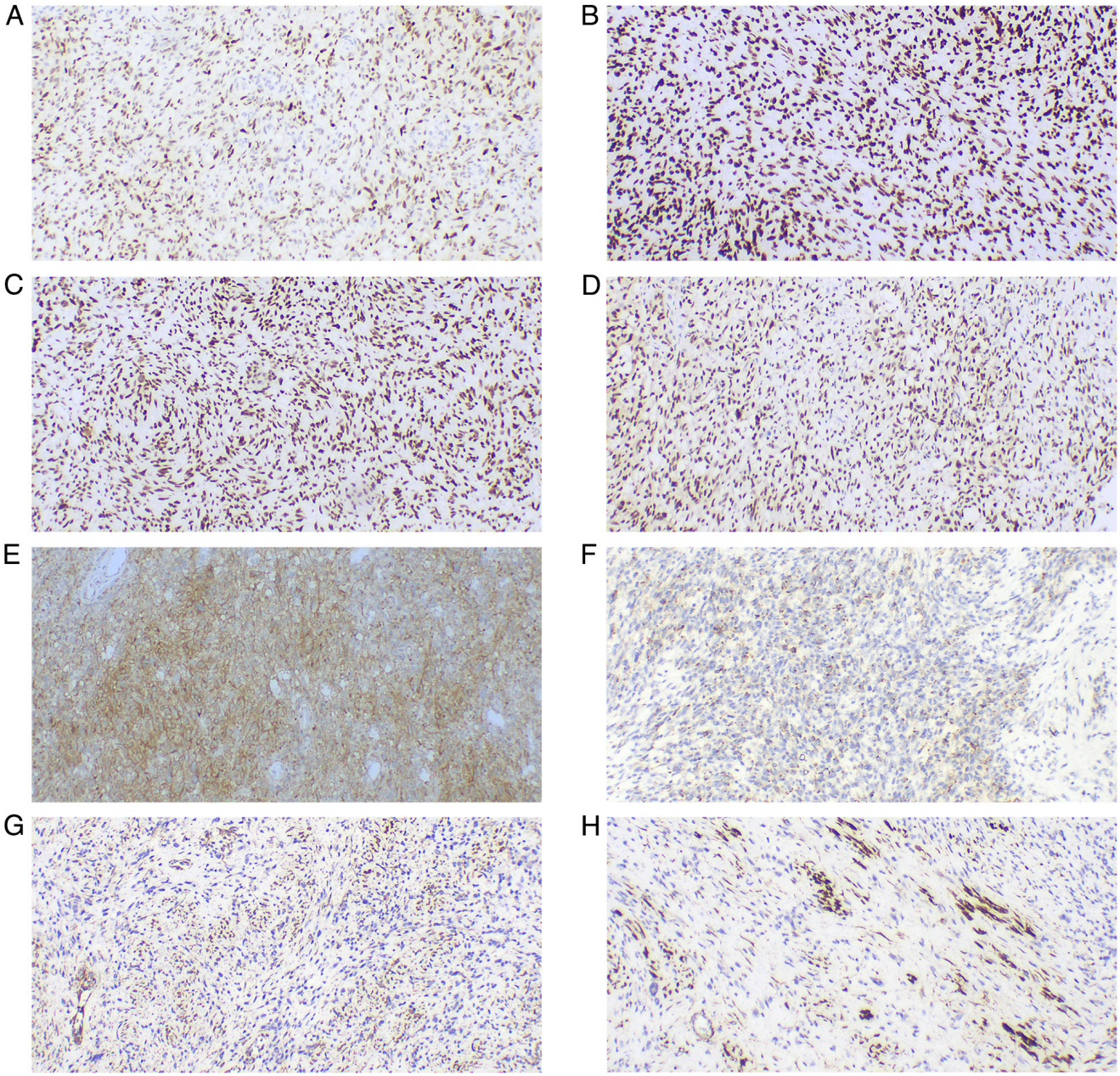

Figure 5. Immunohistochemical characteristics of the cervical malignant peripheral nerve sheath tumor. (A) p53$^+$, (B) Brahma-related gene 1$^+$, (C) integrase interactor 1$^+$, (D) friend leukemia virus integration 1$^+$, (E) CD99$^+$, (F) CD57$^+$ (focal), (G) smooth muscle actin$^+$ (focal) and (H) calponin$^+$ (focal) staining. Magnification, x100.

Schwann cells, with deeply stained and irregular nuclei, round or tapered nuclei, comma or bullet nuclei, easy-to-see mitotic images and mostly elongated wavy cells in the sparse area. In addition, large cells with obvious pleomorphism and multinucleated giant cells were commonly seen in one-third of MPNST cases. Geographic necrosis was also observed in two-thirds of MPNST cases. The tumors are rich in thick-walled blood vessels and focal multidirectional differentiation, such as chondro-osteoid differentiation, rhabdomyoblastic differentiation or angiosarcomatoid differentiation, is found in 10-15% of cases (17,19).

The morphological characteristics of MPNSTs can aid in diagnosing the tumors as malignant, but they need to be differentiated from other smooth muscle, neurogenic and mesenchymal malignancies. Therefore, immunohistochemistry is important, as the best known marker, S-100, is expressed in 50-90% of MPNSTs (20), but it is usually expressed locally (19). The higher the degree of malignancy of the tumor, the more primitive the cell differentiation is and the lower the expression rate of S-100 (21,22). Tumor cells also tend to express Vimentin, SOX-10 and p53, and can express CD56, CD57, PGP9.5 and other neuropathic markers, with a Ki67 index of 5-65%. The morphological and immunohistochemical phenotypes in the present case were consistent with the diagnosis of MPNST. Dense and intermingled spindle cells were accompanied by numerous mitotic and multinuclear giant cells. Bleeding and necrosis were observed in certain areas. The cells were positive for S-100, SOX-10 and CD99, and neural markers, such as CD56 and PGP9.5, were also positively expressed, with a Ki67

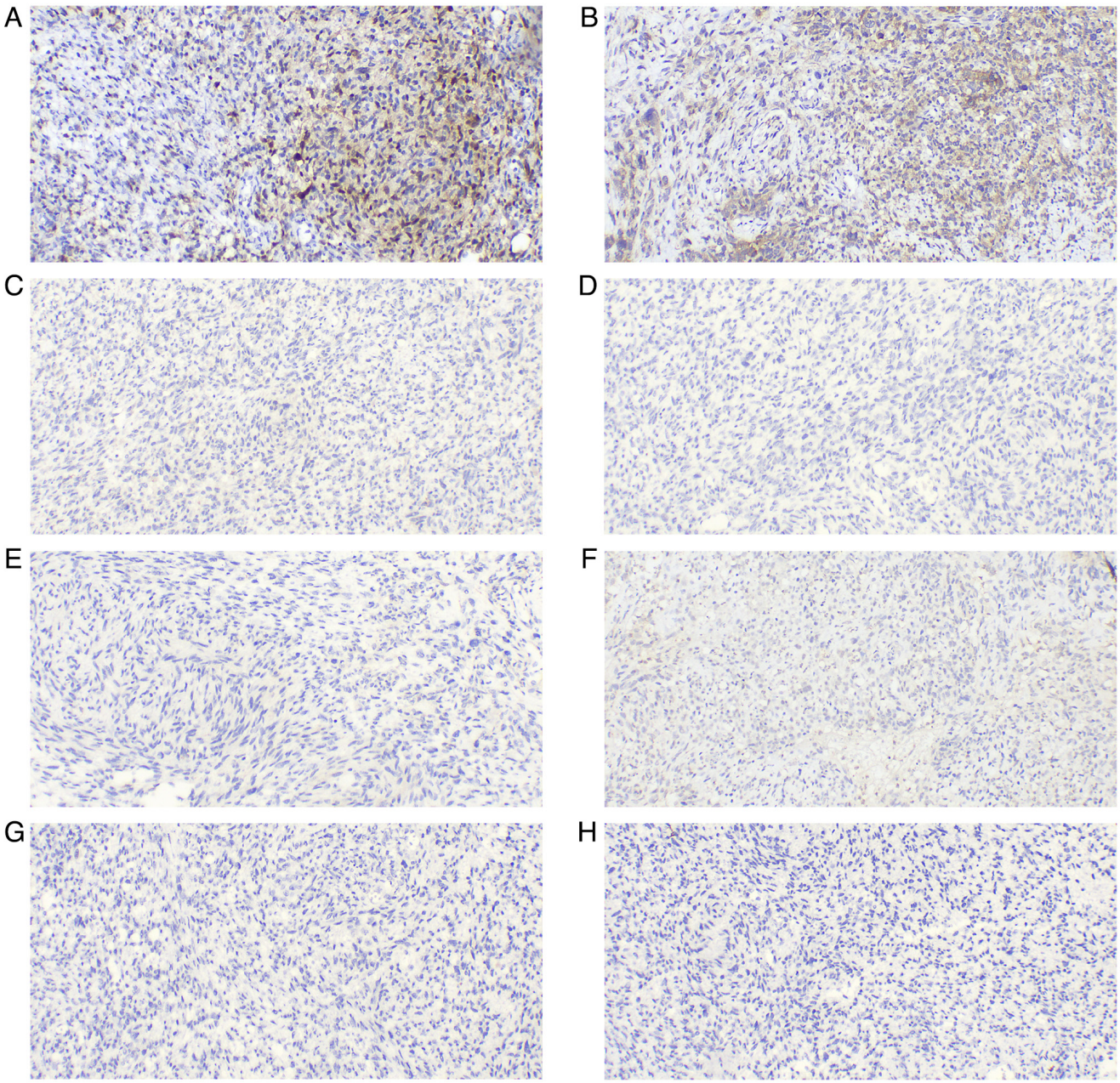

Figure 6. Immunohistochemical characteristics of the cervical malignant peripheral nerve sheath tumor. (A) Cyclin D1^{+} (focal) and (B) anaplastic lymphoma kinase^{+} (focal) staining. (C) Melanoma antigen^{-}, (D) glial fibrillary acidic protein^{-}, (E) epidermal growth factor receptor^{-}, (F) signal transducer and activator of transcription 6^{-}, (G) epithelial membrane antigen- and (H) cytokeratin-pan^{-} staining. Magnification, x100.

index of 20-50%. Both smooth muscle and melanin markers were negative, further confirming the diagnosis of MPNST in the patient.

However, several malignant tumors composed of spindle cells can occur in the cervix, creating the need for a differential diagnosis (2,13). These malignant tumors include the following: i) Spindle cell leiomyosarcoma (LMS) is composed of intersecting long bundles of spindle cells with eosinophilic cytoplasm and rod-shaped, cigar-shaped nuclei or nucleolar vacuoles. This tumor has moderate-to-significant nuclear atypia and high mitotic activity. The diagnosis of LMS requires the immunoreactivity of tumor cells to smooth muscle markers, such as desmin, caldesmon or SMA. ii) Low-grade endometrial stromal sarcomas have infiltrating edges and extensive invasion of the muscular layer. The tumor cells are relatively uniform in size and shape, with round or ovoid nuclei, obscure nucleoli and unclear cell borders. Certain cases may be dominated by spindle cells. This tumor expresses ER, PR, CD10 and vimentin. iii) Adenosarcoma is a low-grade malignant tumor consisting of benign glands and malignant stroma, with a characteristic lobular tumor structure. Tumor cells form a cuff-like structure around the gland. The sarcomatous component can overgrow benign glands, known as 'sarcomatous overgrowth'. It can be distinguished from other cervical sarcomas by its morphological features after extensive sampling. iv) Malignant melanomas have several histological forms, the most common of which are

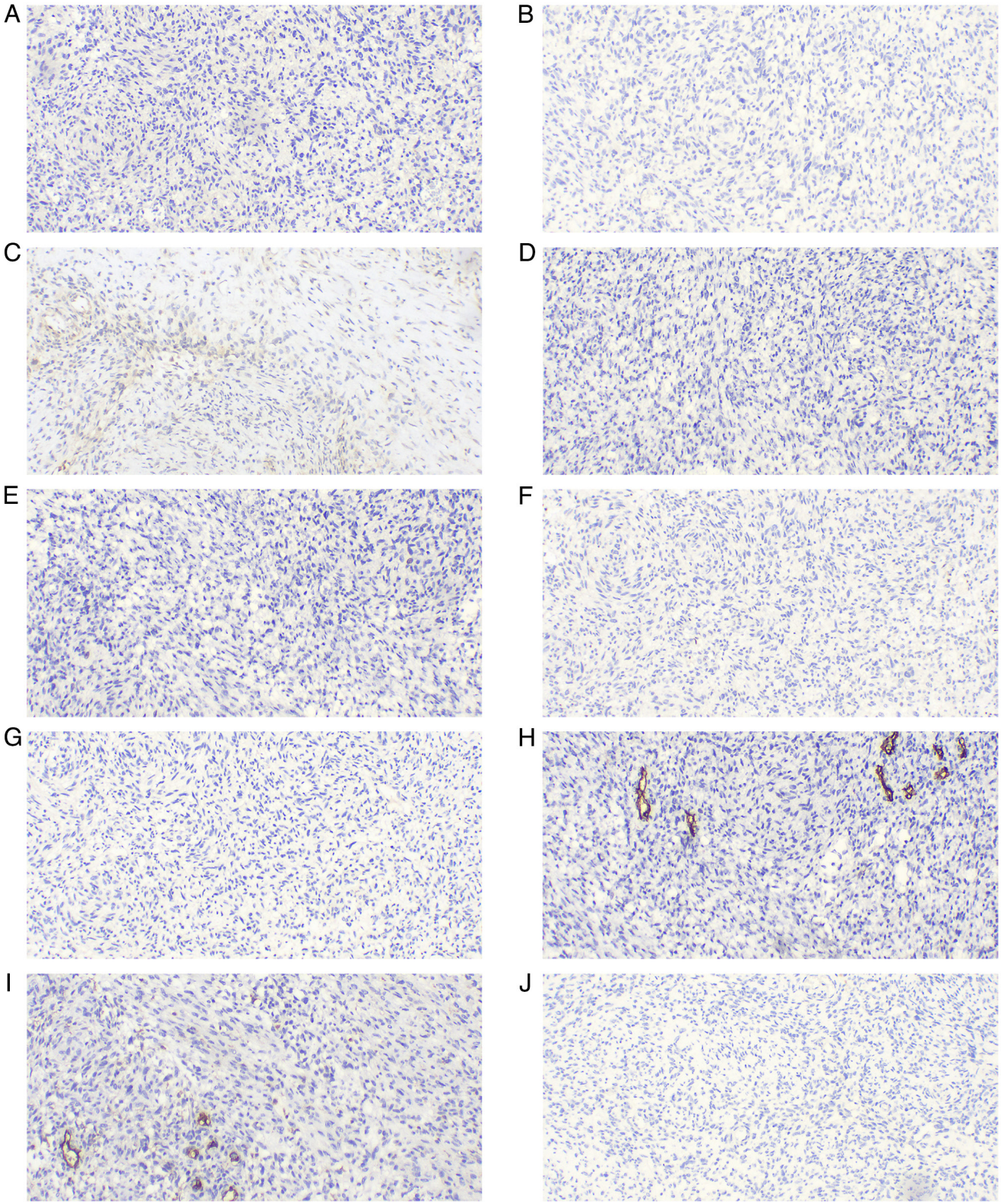

Figure 7. Immunohistochemical characteristics of the cervical malignant peripheral nerve sheath tumor. (A) Caldesmon$^-$, (B) CD10$^-$, (C) B-cell lymphoma 6-corepressor$^-$, (D) myogenin$^-$, (E) myogenin myoblast determination protein 1$^-$, (F) estrogen receptor$^-$, (G) progesterone receptor$^-$, (H) CD34$^-$, (I) CD31$^-$ and (J) tyrosine receptor kinase$^-$ staining. Magnification, x100.

spindle cell type (desmoplastic type) and epithelioid cell type. Pigment is only found in ~50% of the tumors. The tumor cells usually have different degrees of pleomorphism, very active nuclear division and common nuclear and cytoplasmic inclusion bodies, and a few cases can also be seen as multinucleated giant cells. HMB-45, Melan-A and S-100 are commonly expressed in malignant melanomas, but certain cases are negative for melanocytic markers (2,13).

The treatment for cervical MPNST is an abdominal hysterectomy with bilateral salpingo-oopherectomy (23).

Table I. Clinicopathological characteristics of all cervical malignant peripheral nerve sheath tumors reported in the literature.

First author/s, year	Age, years	Symptom	Tumor size, cm	Mitotic figures	Immunohistochemistry results	Neurofibromatosis-1 diagnosis	Pregnancy history	(Refs.)
Sloan, 1988	47	Vaginal bleeding	4x3x2	Numerous mitoses	S-100$^-$	NA	G3P2	(5)
Junge *et al*, 1989	45	Vaginal bleeding	1.2x1x1	Scattered mitotic figures	S-100$^+$ (focal), vimentin$^+$, desmin and CK$^-$	NA	G?P2	(6)
Keel *et al*, 1998	25	Found a cervical polyp	1.3	Easily found mitotic figures	S-100$^+$, vimentin$^+$, desmin$^-$, SMA$^-$, CK$^-$ and HMB45$^-$	NA	NA	(7)
	65	Vaginal bleeding	4.4x2.5x1.4	Easily found mitotic figures	S-100$^+$, SMA$^-$, CK$^-$ and HMB45$^-$	NA	NA	
	73	Vaginal bleeding	5x5	Easily found mitotic figures	S-100$^+$, vimentin$^+$, desmin$^-$, SMA$^-$, CK$^-$ and HMB45-	NA	NA	
Lallas *et al*, 1999	51	Vaginal bleeding	3x3	10 per 10 HPF	S-100$^-$, vimentin$^+$ and SMA$^-$	NA	G3P2	(8)
Bernstein *et al*, 1999	65	Postcoital bleeding	4.4x2.5x1.4	6-10 per 10 HPF	S-100$^+$, CK$^-$ and HMB45$^-$	No	G1P1	(9)
Di Giovannantonio *et al*, 2005	27	Vaginal bleeding	NA	High mitotic rate	S-100$^+$, vimentin$^+$, desmin$^-$, CK$^-$ and HMB45$^-$	NA	NA	(10)
Rodriguez *et al*, 2006	22	Postcoital bleeding	3	Average 2-3 per 10 HPF, ≤6 per 10 HPF	S-100$^+$, CD10$^-$, desmin$^-$, SMA$^-$, HMB45$^-$ and Melan-A$^-$	NA	G?P0	(11)
Kim *et al*, 2009	50	Vaginal bleeding	6x3.5x2	Abundant mitotic figures	S-100$^+$ (focal), desmin$^-$, SMA$^-$, HMB45$^+$ (focal) and Melan-A$^-$	NA	G4P4	(12)
Mills *et al*, 2011	32	Found a cervical polyp	2	2 per 10 HPF	S-100$^+$ (focal), vimentin$^+$, CD34$^+$ (70%), desmin$^-$ and HMB45$^-$	No	NA	(13)
	60	Vaginal bleeding	5.8	≤3 per single HPF	S-100$^+$ (focal), vimentin$^+$, CD34$^+$ (50%), desmin$^-$ and HMB45$^-$	No	NA	
	25	Vaginal bleeding	8	≤4 per single HPF	S-100$^+$ (focal), vimentin$^+$, CD34$^+$ (<10%), desmin$^-$ and HMB45$^-$	No	NA	
Akhavan *et al*, 2012	53	Purulent, malodor vaginal discharge	7	Scattered mitotic figures	S-100$^+$, vimentin$^+$, desmin$^+$ (focal), CK$^-$ and HMB45$^-$	No	G12P11	(14)

Table I. Continued.

First author/s, year	Age, years	Symptom	Tumor size, cm	Mitotic figures	Immunohistochemistry results	Neurofibromatosis-1 diagnosis	Pregnancy history	(Refs.)
Dong *et al*, 2014	45	Vaginal bleeding	3.7x2.6	Scattered mitotic figures	$S\text{-}100^{+}$	NA	NA	(15)
Sangiorgio *et al*, 2018	45	Vaginal bleeding	4	≤40 mitoses per 10 HPF	$S\text{-}100^{+}$, $CD34^{+}$ (10%), $CD10^{-}$, $desmin^{-}$, SMA^{-} and $HMB45^{-}$	No	G4P2	(2)
Zhang *et al*, 2022	46	Vaginal bleeding	NA	NA	$S\text{-}100^{+}$, $vimentin^{+}$, CK^{-} and $CD34^{-}$	No	G?P2	(16)
Current case	35	Vaginal bleeding	4x3.5x2	≤30 mitoses per 10 HPF	$S\text{-}100^{+}$, $vimentin^{+}$, $desmin^{-}$, CK^{-}, $HMB45^{-}$ and $Melan\text{-}A^{-}$	No	G1P1	-

NA, not available; HPF, high-power field; CK, cytokeratin; SMA, smooth muscle actin; HMB-45, human melanoma black-45; Melan-A, melanoma antigen; G, gestation; P, parturition; ?, unknown.

As lymph node metastasis is rare, a pelvic lymph node dissection may or may not be performed. If there is a need for fertility in young, nulliparous patients, a radical vaginal trachelectomy may be attempted (11). High-dose radiotherapy is recommended for tumors ≥5 cm with microscopically positive incisal margins (24). Chemotherapy is beneficial for survival and for the prevention of metastasis in patients with MPNST (25). Kroep *et al* (26) reported that doxorubicin-IFO regimens were superior to other regimens for MPNSTs. However, there is no specific clinical treatment plan. The chemotherapy plus radiotherapy plan adopted for the patient in the present case was a trial treatment, with IFO, VP16 and DDP being common chemotherapy drugs for the treatment of malignant tumors. Adjuvant radiotherapy was added to prevent recurrence, as the tumor deeply infiltrated the cervical stroma.

In conclusion, cervical MPNST is rare, and the morphological and immunohistochemical phenotypes overlap with several types of cervical tumor. During diagnosis, attention should be given to adequate sampling, careful observation of the morphology under the microscope and adequate immunohistochemistry for a potential differential diagnosis.

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Availability of data and materials

All data used and/or analyzed during this study are included in this published article. Due to patient privacy concerns and the data protection, the NGS data has not been submitted to a public repository.

Authors' contributions

XL was responsible for collecting the clinical and pathological data of the patient, for study conception and for writing the manuscript. LL contributed to the analysis of the case data and revision of the manuscript. XL and LL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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