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Case Report

Myxoid endometrial stromal sarcoma: report of two cases with emphasis on its diagnostic problems

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Abstract: Aims: To address the diagnostic problems of uterine myxoid endometrial stromal tumor. Methods: We investigated the clinicopathologic and immunohistochemical features of 2 myxoid endometrial stromal sarcomas. Results: Patient 1 had a recurrent pelvic tumor. She had a history of abdominal hysterectomy for "uterine multiple leiomyomas" 3 years ago. The pelvic tumor and her previous uterine tumor were both composed of myofibroblast-like spindle cells, and small oval cells in a myxoid matrix. The mitotic figures were up to 3-4/10 HPFs. There were numerous small thin-walled vessels and anastomosing capillaries. Patient 2 had a gelatinous polypoid mass in the uterine cavity. The tumor harbored plump spindle tumor cells loosely embedded in the prominent myxoid matrix. It morphologically mimicked an inflammatory myofibroblastic tumor. However, it had a tongue-like myometrial invasion and vascular involvement. By immunohistochemistry, the tumor cells in both cases were all positive for CD10, and negative for caldesmon, CD117, CD34 and ALK. Conclusions: Endometrial stromal tumors can show a substantial myxoid component. Careful morphologic assessment and immunohistochemical study will contribute to their distinction from myxoid leiomyosarcoma, inflammatory myofibroblastic tumor and other morphologic mimickers.

Keywords: Endometrial stromal sarcoma, myxoid, pathology, immunohistochemistry, uterus

Introduction

Endometrial stromal tumor is an uncommon uterine tumor [1]. There are four types of endometrial stromal tumors: the endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), and undifferentiated uterine sarcoma, according to the World Health Organization (WHO) classifications of tumors of the female genital tract. LGESS is a morphologically bland tumor resembling proliferative phase endometrial stromal cells, and can be distinguished from ESN by an infiltrative tongue-like growth pattern and vascular invasion. High-grade ESS is characterized by high-grade, small round cells and sometimes associated with LGESS. The diagnosis of ESS with unusual morphologic features is difficult, including sex-cord like and smooth muscle differentiation, a fibrous or myxoid appearance, extensive endometrial glandular differentiation, and a pseudopapillary architecture. Among these unusual variants, myxoid ESS is extremely rarely reported to date [3]. In this study, we report 2 myxoid endometrial stromal sarcomas to emphasize its differential diagnosis with its morphologic mimickers.

Materials and methods

Patient records were obtained from the electronic files of our hospital. This study was conducted with the approval of the hospital's Institutional Review Board. The patients or their relatives gave informed consent. Clinical details were retrieved from the hospital's electronic medical record. The follow-up data were obtained by phone communication with the patients. The archival hematoxylin-and-eosin (H&E) slides were reviewed by the authors. The mitotic figures were recorded as the average number of 10 high power fields (HPF) (40×, HPF = 0.55 mm in diameter) by counting 40 hotspot HPFs.

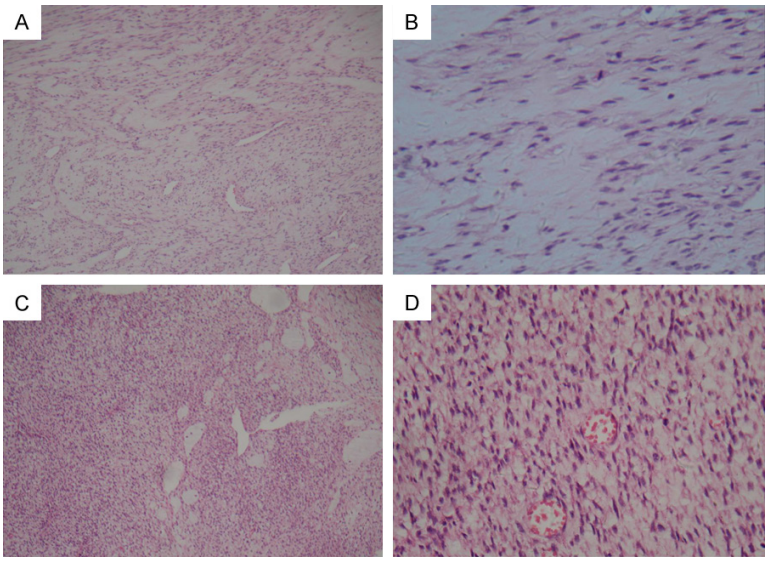

Figure 1. Histopathology of Case 1. The tumor is mainly composed of myofibroblast-like spindle cells (A, B) and small oval cells resembling the proliferative-phase endometrium (C, D) along with a prominent myxoid stroma. Mitotic figures can be seen in the tumor cells (B, D). Original magnifications: (A, C) ×100; (B, D) ×200.

The formalin-fixed, paraffin embedded blocks were cut at 4 μm. Alcian blue (pH 2.5) staining was carried out. A two-step EnVision immunostaining procedure (DAKO, Carpentaria, CA, USA) was performed according to the manufacturer's protocol. The antibodies were products of DAKO (Carpenteria, CA, USA). They were used as follows: CD10 (56C6; dilution 1:100), caldesmon (h-CALD, 1:200), Desmin (D33, 1:100), α-smooth muscle actin (1A4; 1:200), Cyclin D1 (CCND1; SP4, 1:50), Ki67 (MIB-1, 1:300), ALK (D5F3, ready-to-use), S100 (polyclonal, 1:2000), CD34 (QBEnd 10, 1:200), CD117 (polyclonal, 1:200), estrogen receptor (ER; 1D5; 1:300), and progesterone receptor (PR; 1A6; 1:500). The percentage of positive cells was scored as follows: - for no immunoreactivity (-); focally staining for 1% to 10% (+); staining for > 10% (++) and strong positivity for > 30% (+++). Ki67 index was recorded as the percent of positive cells in 10 HPFs from the hotspots.

Results

Patient 1

Patient 1 (gravida 5, para 1) was 46 years old. She was admitted to our hospital due to the presence of a pelvic mass for more than one year and lower abdominal pain for more than one month. Pelvic examination revealed an irregular mass on the top of the cervical stump. Transvaginal ultrasonography indicated a lobulated mass with a size of 8.8*4.9*4.6 cm^3 on the right-up side of the cervical stump. She had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) 3 years ago. The pathologic diagnosis was "uterine multiple leiomyomas" at that time. At operation, an irregular, lobulated mass was found between the rectum and the bladder. It showed an infiltrative growth towards the top and posterior wall of the bladder. The mass was completely removed. She received one course of chemotherapy (vincristine, adriamycin, and dexamethasone, VAD) after her surgery, but she refused further treatment. She was lost to follow-up 6 months later.

Grossly, a lobulated mass measured 13.5*13*12 cm^3 in size. On sectioning, the tumor was grayish-white and gelatinous, and focally yellowish. Histopathologic examination showed that the tumor was mainly composed of myofibroblast-like spindle cells and small oval cells resembling the proliferative-phase endometrium in the context of the prominent myxoid stroma (**Figure 1A-D**). The spindle tumor cells had slightly eosinophilic cytoplasm, mild nuclear atypia, and few mitotic figures (~1/10 HPFs) while the oval cells showed high nucleus: cytoplasm ratio, hyperchromatic nuclei and increased mitotic figures (3-4/10 HPFs). There were numerous small thin-walled vessels and anastomosing capillaries but spiral arterioles surrounded by neoplastic cells were absent. Approximately 30% area of the tumor showed smooth muscle differentiation, which was characterized by fascicles of long spindle cells with abundant eosinophilic cytoplasm and cigar-shaped nuclei with blunt ends. The tumor showed an invasive growth towards the surrounding smooth muscle bundles which were probably from the bladder wall.

A review of the slides of the uterine tumor from her first surgery showed a similar morphology

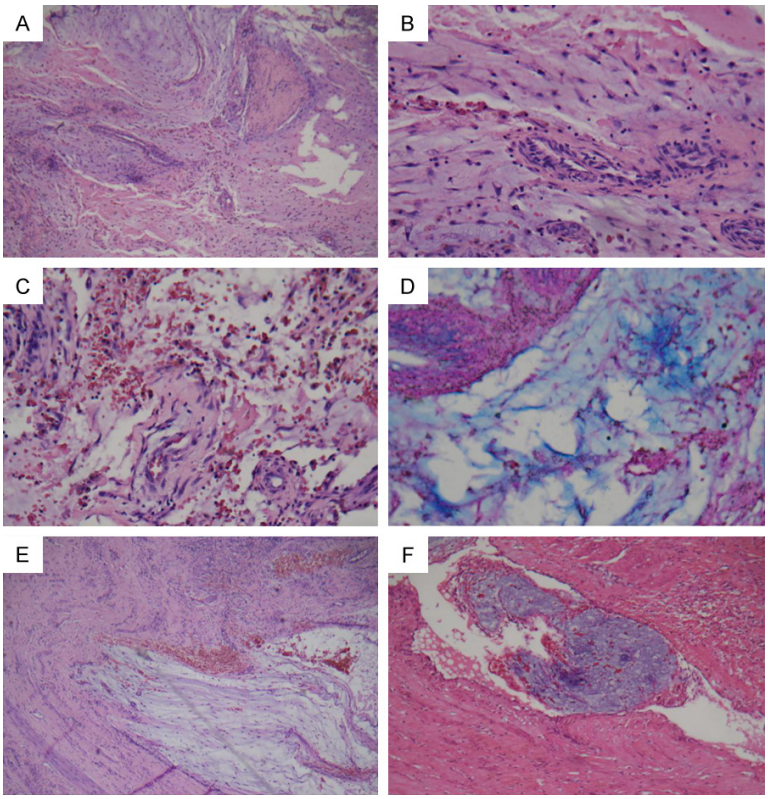

Figure 2. Histopathology of Case 2. The plump spindle tumor cells are loosely embedded in the rich myxoid stroma, mimicking an inflammatory myofibroblastic tumor (A, B). Some thin-walled blood vessels resemble spiral arterioles surrounded by tumor cells (C). The myxoid stroma is Alcian blue (pH2.5) + (D). The typical tongue-like myometrial (E) and vascular invasion (F) can be seen. Original magnifications: (A, F) ×100; (B-D) ×200; (C) ×25.

and immunohistochemistry, but the tumor borders could not be assessed because the interface between the tumor and uterine myometrium was unavailable. The patient was eventually diagnosed with recurrent myxoid ESS with smooth muscle differentiation.

Patient 2

A 51-year-old patient, gravida 2, para 1, complained of abnormal vaginal discharge for more than one year. Transvaginal ultrasonography showed a hypoechoic mass with a diameter of 7.4 cm in the uterine cavity and endocervical tube. A pre-operative curetting suggested a myxoid mesenchymal tumor with low malignant potential. The patient underwent TAH-BSO. Her clinical course was uneventful. She lived without evidence of disease up to 37 months at present.

Macroscopic examination found that the uterine cavity harbored a grayish-reddish polypoid mass with a size of 6.5*7*4 cm^3. The cut surface was clear and gelatinous, and had a focal hemorrhage. The tumor was ill-demarcated from the uterine myometrium. On microscopic examination, the whole tumor, either from her endometrial curetting or hysterectomy, had predominantly myxoid stroma. The plump spindle tumor cells were loosely distributed in the myxoid stroma (**Figure 2A**, **2B**). They had mild atypia and rare mitotic figures (1-2/10 HPFs). The cytoplasm was slightly basophilic. Thin-walled blood vessels were abundant, some of which resembled spiral arterioles surrounded by tumor cells (**Figure 2C**). The myxoid stroma was Alcian blue (pH 2.5) + (**Figure 2D**). Hemosiderin-laden macrophages, lymphocytes, and neutrophils were apparent in the tumor. The tongue-like invasion of the myometrium (**Figure 2E**) and vascular invasion (**Figure 2F**) was present. The case was consistent with low grade ESS with extensive myxoid changes.

Clinical features of 2 myxoid endometrial stromal sarcomas are shown in **Table 1**.

Immunohistochemistry

The cases showed relatively consistent immunohistochemical features (**Table 2**). In patients 1 and 2, the tumor cells were strongly immunoreactive for CD10 (**Figure 3A**, **3B**), and negative for desmin, caldesmon, CD117, CD34 and ALK1. Diffuse Cyclin D1 staining was present in case 1 (**Figure 3C**). The Ki67 index ranged from 5% to 10%.

Discussion

Oliva and colleagues first reported 4 ESSs with an extensive myxoid component in 1999 [2]. Their extensive review of earlier literature indicated very limited references to extensive myxoid change in ESS. They suggested that uterine fibromyxosarcoma in the old literature was most appropriately reclassified as ESS. However, only two myxoid ESSs were reported in the

Table 1. Clinical features of 2 myxoid endometrial stromal sarcomas

Case #	Age	G&P	Clinical Presentations	Tumor site (cm)	Clinical History	Original Diagnosis	Final diagnosis	Clinical Procedures	Follow up (mo.)
1	46	G5P1	Lower abdominal pain	Pelvic mass (9*5*4)	TAH	Myxoid leiomyoma	Myxoid HGESS	Removal of pelvic mass and dissection of pelvic lymph nodes	LFU (6)
2	51	G2P1	Vaginal discharge	Uterine cavity and endocervix (4*3*3)	Curetting	Myxoid mesenchymal tumor with low malignant potential	Myxoid LGESS	TAHBSO	ANED (37)

Abbreviations: ANED, Alive with no evidence of disease; AUB, Abnormal uterine bleeding; LFU: loss of follow up; LGESS, low grade uterine endometrial stromal sarcoma; mo., months; TAHBSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Table 2. Immunohistochemical features of 2 myxoid endometrial stromal sarcomas

Case #	CD10	S100	ER	PR	SMA	Des	Caldes	CCND1	Ki67	CD34	CD117	ALK
1	+++	++	-	-	+	-	-	++ 50%	10%	-	-	-
2	+++	+	+	+	-	-	-	+	5%	+	-	-

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; SMA, smooth muscle actin; Des, desmin; Caldes, caldesmon; CCND1, cyclin D1; ALK, anaplastic large cell lymphoma kinase.

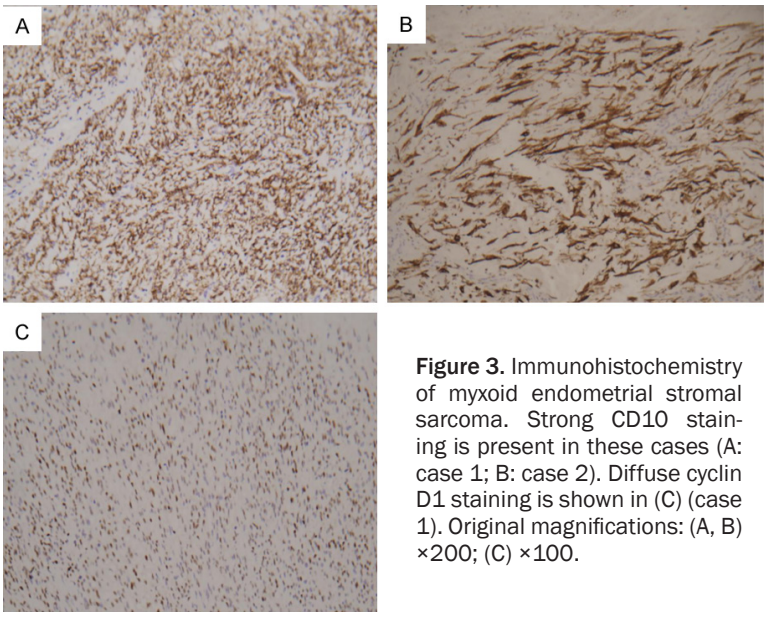

Figure 3. Immunohistochemistry of myxoid endometrial stromal sarcoma. Strong CD10 staining is present in these cases (A: case 1; B: case 2). Diffuse cyclin D1 staining is shown in (C) (case 1). Original magnifications: (A, B) ×200; (C) ×100.

English literature thereafter [3, 4]. The frequency of myxoid ESS appears underestimated. In this study, we report 2 similar cases with other unusual features. Our observations will expand recognition of this rare endometrial stromal tumor.

Patient 1 had a recurrent tumor containing a substantial part of spindle cells and abundant myxoid stroma. It should be distinguished from a myxoid leiomyosarcoma. Both myxoid ESS and leiomyosarcoma shared overlapping morphologic features [5, 6], resulting in diagnostic difficulties. The presence of the prominent vasculature, particularly small arterioles, is a helpful morphologic indicator for myxoid ESS. Moreover, ESS frequently demonstrated strong CD-10 expression and weakly positive or negative staining of SMA, desmin, and h-caldesmon [1, 6-8]. A recent study described a novel HGESS, mimicking a myxoid leiomyomsarcoma morphologically and harboring ZC3H7B-BCOR gene fusions [9]. It was predominantly composed of spindle cells with focal fascicular areas and extensive myxoid changes. The tumors displayed delicate thin-walled capillaries, but lacked whirling of tumor cells. Mitotic figures varied from 3-4/10 HPFs to > 10/10 HPFs. The tumors were strongly positive for CD10 and focal positive for SMA. The morphology and immunohistochemistry of our case were consistent with the novel HGESS.

Patient 2 had mostly myxoid change throughout the tumor. In addition to myxoid leiomyosarcoma, other myxoid mesenchymal tumors of the uterus should enter into the differential diagnosis. The discrimination from inflammatory myofibroblastic tumor is paramount because of their different clinical treatment and outcomes [10, 11]. Inflammatory myofibroblas-

tic tumor is composed of plump spindle cells in a prominent myxoid matrix and a mixed inflammatory infiltrate. The tumor frequently harbors the rearrangement of Anaplastic Lymphoma Kinase (ALK) gene (2p23), which is highly correlated with ALK expression by immunohistochemistry [10, 11]. A heavy infiltrate of inflammatory cells in our case critically raised the possibility of inflammatory myofibroblastic tumor. However, we believe that the heavy inflammatory change and numerous hemosiderin-laden macrophages might be caused by the recent endometrial curettage. The abundant arterioles with occasional whirled tumor cells, the tongue-like myometrial invasion and vascular involvement are strong indicators for an ESS. These classical immunohistochemical features (strong CD10 expression and negative ALK) can confirm the diagnosis of ESS. Other mesenchymal tumors with myxoid changes, such as malignant nerve sheath tumor, and liposarcoma, rarely occur in the uterus, and can readily be discriminated from myxoid ESS by the high grade morphology and specific immunohistochemistry.

In summary, myxoid endometrial stromal tumors are rare, but they can show a variety of morphologic alterations. These tumors should be distinguished from myxoid leiomyosarcoma, inflammatory myofibroblastic tumor and other myxoid mesenchymal tumors involving the uterus. The differential diagnosis is critical but extremely difficult. Careful morphologic assessment with the aid of a panel of antibodies including CD10, SMA, caldesmon, and ALK, is generally sufficient for a correct diagnosis. Further investigation should be encouraged to discover the distinct molecular features, the proper clinical intervention and prognostic indicators in this rare endometrial stromal tumor.

Disclosure of conflict of interest

None.

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