

## Original Article

# Endometrial stromal sarcoma: a clinicopathological analysis of 14 cases

Fuqiang Wang\*, Ruixue Lei\*, Haijun Yang, Mei Guo, Gaimin Tan

Anyang Tumor Hospital, Anyang, Henan, China. \*Equal contributors and co-first authors.

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**Abstract:** Objective: To investigate the clinicopathologic features and immunophenotype of endometrial stromal sarcoma (ESS) and extra uterine endometrial stromal sarcoma (EESS). Methods: 14 cases of ESS (8 cases of ESS and 6 cases of EESS) were retrospectively reviewed, and the pathological features, immunophenotype and prognosis were discussed. Results: In 14 cases of ESS, 12 cases (8 cases of ESS and 4 cases of EESS) were diagnosed as low grade endometrial stromal sarcoma (LGESS) and 2 cases of EESS were diagnosed as high grade endometrial stromal sarcoma (HGESS). Microscopically, the tumor cells in LGESS cases were composed of densely arranged endometrial stromal cells with a similar proliferative phase. They were surrounded by spiral arterioles and mitosis was rare. The tumor cells in HGESS cases displayed marked cellular atypia, increased mitosis, infiltration, and necrosis. However, small blood vessels which were common in LGESS were rarely observed in HGESS. Immunohistochemical results showed that most tumor cells were positive for CD10, vimentin, PR, and ER. Conclusions: ESS is a rare tumor in the female genital tract and is often misdiagnosed as other mesenchymal tumors before operation. The diagnosis mainly depends on the clinicopathologic features together with the immunophenotype. LGESS has better long term survival and lower incidence of disease recurrence than HGESS. Thus, LGESS has better prognosis than HGESS.

**Keywords:** Endometrial stromal sarcoma, extra uterine endometrial stromal sarcoma, uterine tumor, immunohistochemistry

## Introduction

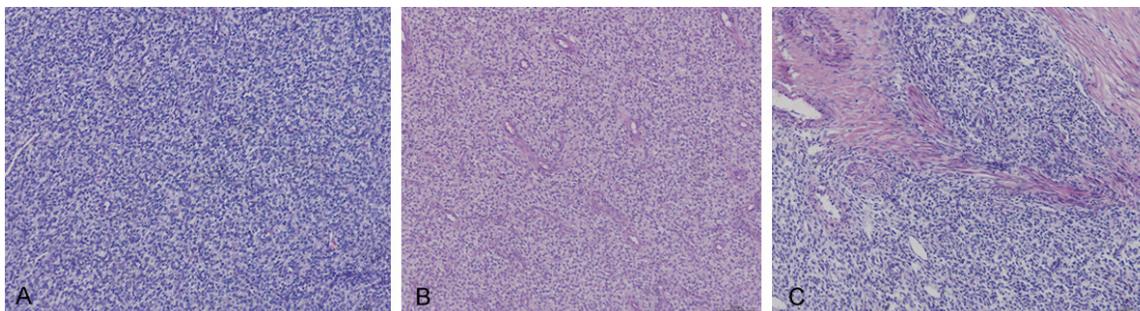
Endometrial stromal sarcoma (ESS) is a rare malignant tumor of the female genital tract, which originates from endometrial stromal cells and occurs frequently in the uterine cavity. Extra uterine endometrial stromal sarcoma (EESS) is rare, which originates from malignant transformation of endometriosis or malignant transformation of pelvic primordial Mullerian cells [1-5]. The World Health Organization (WHO) [6] currently divides these endometrial stromal tumors into four different subtypes based on clinical and pathologic features: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcomas (LGESS), high-grade endometrial stromal sarcomas (HGESS), and undifferentiated endometrial sarcoma (UUS). These categories are defined by the presence of distinct translocations as well as tumor morphology and prognosis. LGESS is more common than HGESS and LGESS is gen-

erally a low-grade malignant neoplasm with an indolent clinical course and has a better prognosis. HGESS is a high-grade malignant neoplasm with rapid development, easy recurrence, and prevalent metastasis, thus resulting in a poor prognosis. This review discusses the clinicopathologic features, immunohistochemical diagnosis and differential diagnosis of this ESS in order to improve the understanding of the tumor.

## Materials and methods

The clinical and pathological data of 14 patients with ESS diagnosed by Pathology Department of Anyang Tumor Hospital from January 2010 to December 2015 were retrospectively analyzed and all cases were confirmed by at least two senior pathologists. According to the lesion site, all the cases were divided into two groups: uterine origin of endometrial stromal sarcoma (ESS) and extra uterine endometrial stromal

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**Figure 1.** A. H&E  $\times 100$  staining shows that the tumor cells are small, oval to fusiform, imparting a monotonous appearance and similar to the endometrial stromal cells in proliferative phase; B. The tumor cells are spirally arranged around the small vessels with H&E  $\times 100$  staining; C. The tumor is infiltrated in the myometrium as irregular tongue shape with H&E  $\times 100$  staining.

sarcoma (EES). Comparisons were made regarding the clinical and pathological characteristics of the two groups.

The specimen was fixed in 4% buffered formalin, routinely processed, with tissue sections embedded in paraffin. The sections were cut at 4  $\mu\text{m}$  in thickness and were stained with hematoxylin and eosin (H&E). Immunohistochemistry was performed according to standard protocols. The following antibodies were used: estrogen receptors (ER) (Dako Denmark, prediluted), progesterone receptors (PR) (Dako Denmark, prediluted), Vimentin (Dako Denmark, prediluted), CD10 (Dako Denmark, prediluted), HMB45 (Dako Denmark, prediluted), MIB1/Ki67 (Dako Denmark, prediluted), Desmin (Dako Denmark, prediluted), H-caldesmon (Dako Denmark, prediluted), Inhibin (Dako Denmark, prediluted), CD34 (Dako Denmark, prediluted), Calretinin (Dako Denmark, prediluted), CD99 (Dako Denmark, prediluted), EMA (Dako Denmark, prediluted). All negative and positive controls were included. The specific part of the tumor cells were stained as brown and yellow, which was considered as positive expression. CD10, CD34, and EMA were stained on cell membrane. Vimentin, H-caldesmon, desmin, inhibin, calretinin, CD99 and HMB45 were stained in the cytoplasm. ER, PR, and Ki67 were stained in the nucleus.

### Results

#### *Clinical data*

14 cases of ESS patients, the average age was 53.5 years old (ranged from 31 to 76 years old). All of them have offspring, 8 of them have gone

through menopause. Five cases complained vaginal bleeding after menopause, 3 cases showed lower abdominal pain, 6 cases showed pelvic mass. Physical examination: The uterine origin of endometrial stromal sarcoma in 8 patients had different degrees of increase in the uterus. Ultrasound showed low or medium echo mass in the uterine wall, or the uterine cavity, and internal echo was heterogeneous. The extra uterine endometrial stromal sarcoma in 6 patients showed pelvic low mass. The pre-operative clinical diagnosis was uterine fibroids or pelvic mass.

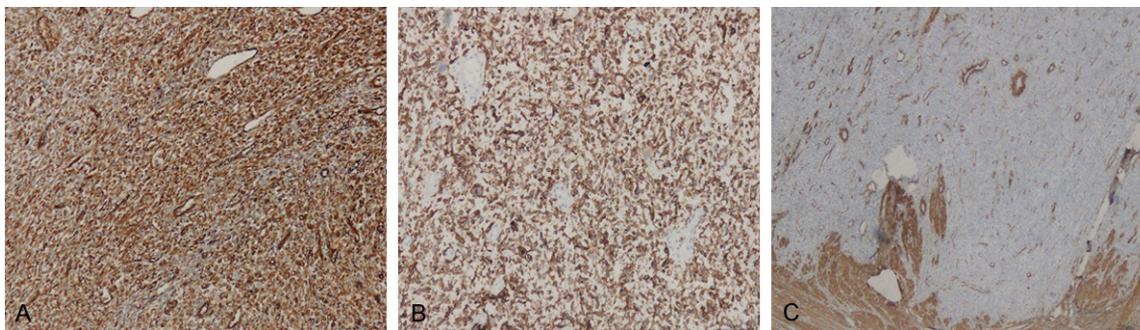
#### *Gross examination*

Tumors in 8 cases were confined to the uterus, and no significant metastasis out of the uterus was observed. All the tumors had infiltrated into the uterine wall, and 6 of them protruded into the uterine cavity. The other 6 cases showed migration out of the uterus, with 3 cases in the pelvic cavity, 1 case in the mesentery, 1 case in the cervix, and 1 case in the peritoneum. The tumor diameters ranged from 6 to 25 cm. The cut surface of the tumor was a soft, tan or gray-white part of the tumor with bleeding and necrosis.

#### *Microscopically*

Eight cases of ESS and 4 cases of EESS were characterized by low-grade endometrial stromal sarcomas. The tumor cells were small, oval to fusiform with a monotonous appearance, and showed similarity to the endometrial stromal cells in proliferative phase (**Figure 1A**), with low cytologic atypia and low mitotic activity. The stroma was rich in endometrial spiral arteri-

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**Figure 2.** Immunohistochemistry of the ESS. A. Diffuse, positive expression of Vimentin; B. Diffuse, positive expression of CD10; C. No expression of H-caldesmon with surrounding myometrium demonstrating positive internal control (IHC with SP method  $\times 100$ ).

oles, and the tumor cells were spirally arranged around the small vessels (**Figure 1B**). When the cells are dense, the blood vessels are not obvious, and the stroma may appear to have hyalinization or to have the starburst appearance. The prominent feature is that the edge of the tumor is infiltrated into the myometrium as irregular tongue shape (**Figure 1C**). Various histologic features of ESS can have an impact on the appearance of the tumor. These include but are not limited to the sex cord structure, and endometrial structure. Smooth muscle, skeletal muscle, fibromyxoid, rhabdoid, epithelioid, myxoid and chondrogenic differentiation features may also be present. Eight cases of ESS showed different degrees of invasion to the surrounding tissue, of which 3 cases showed smooth muscle differentiation. There was a transition between endometrial stromal cells and differentiation of smooth muscle tumor cells. The mitotic figures were visible (3-5 mitoses/10 HPFs), and no abnormal mitotic figures were observed. Two cases of EESS represent characteristics of high-grade endometrial stromal sarcomas. The tumor cells atypia was obvious, and the differentiated interstitial cells were lost, with mucinous cystic degeneration and multiple foci of coagulative necrosis. Mitotic activity was consistently higher ( $>10$  mitoses/10 HPFs) than the traditional LGEES. Only a small number of LGEES components were found in the tumor.

### *Immunophenotype*

Fourteen cases were positive for vimentin (**Figure 2A**), of which 12 cases of LGEES were diffusely positive for CD10 (**Figure 2B**) and 2 cases of HGEES were low-level regional posi-

tive for CD10. Eleven cases were positive for PR and ER. Four cases showed focal expression of Desmin. One case was focal positive for CD99, calretinin, and inhibin. All cases were negative for H-caldesmon (**Figure 2C**), CD34 and EMA. The Ki-67 positive index was 10%-40%.

### *Follow-up*

Twelve cases were successfully followed up, 2 cases were lost. Follow-up time ranged from 1 to 5 years. Two cases of HGEES died from multiple organ and lymph node metastasis 2 years after operation. Three cases relapsed after 4 years, and were followed up for 2 years after re-operation and radiotherapy. No recurrence was observed in the remaining 9 cases.

## **Discussion**

### *Clinical features*

ESS is a rare malignant tumor of the female genital tract, constituting 1%-4% of malignant tumors in the female genital system [7]. ESS originates from the endometrial stroma cells and occurs frequently in the uterine cavity. Extra uterine endometrial stromal sarcoma (EESS) is more rare, occurs in ovary, pelvic cavity, retroperitoneum, mesentery, and originates from malignant transformation of endometriosis or malignant transformation of pelvic primordial Mullerian cells. ESS is more common in middle-aged women (45-55 years old), often with irregular vaginal bleeding and abdominal distension. When ESS is confined to the uterus, it is easy to be misdiagnosed as uterine leiomyoma. Eight case of ESS showed different degrees of increase in the size of uterus. Gross

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examination: All the tumors were infiltrated in the uterine wall, and 6 of them protruded into the uterine cavity. EESS occurred in the menopausal women, often with pelvic masses as the major complaint. Six cases showed pelvic low mass. The cut surface of the tumor was a soft, tan or gray-white, part of the tumor with bleeding, necrosis and cystic. Preoperative fractional curettage and rapid freezing were difficult to be diagnosed before operation. Therefore, the routine histological sections and immunohistochemical staining of ESS are particularly important for the diagnosis.

### *Diagnosis*

The morphology for both ESS and EESS was basically the same. Twelve cases were LGESS, 2 cases were HGESS. The tumor cells are small, oval to fusiform, imparting a monotonous appearance and they are similar to the endometrial stromal cells in proliferative phase, with low cytologic atypia and low mitotic activity. The tumor is rich in endometrial spiral arterioles and is infiltrated in the myometrium as irregular tongue shape. There are different types of differentiation, such as smooth muscle differentiation, fibromyxoid, sex cord differentiation, which make diagnosis and differential diagnosis difficult. Two cases of EESS are characteristics of high-grade endometrial stromal sarcomas. The tumor cell atypia was obvious, and the differentiated interstitial cells were lost, with mucinous cystic degeneration and multiple foci of coagulative necrosis. The mitotic activity was easily visible (>10 mitoses/10 HPFs). At this time, we need more tumor tissues to find the typical LGESS region to diagnose, otherwise we can diagnose UUS. Most tumor cells of LGESS were diffusely positive for CD10, ER and PR, and sometimes they can be negative. In this case, it is important to integrate the morphological feature. Positive expression of ER and PR in 12 cases was helpful for treatment of the corresponding hormone receptor antagonist. Expression of Desmin and SMA was focal positive in the smooth muscle differentiation region, but H-caldesome was negative. The expression of inhibin, calretinin and CD99 was focal positive in the sex cord differentiation region. Expression of CD10, ER, and PR in the HG-ESS were negative but only expressed in the LGESS region.

In all, the histologic and immunohistochemical markers of low-grade extra uterine endometrial stromal sarcoma (LG-EESS) are similar to LGESS. However, due to its occurrence in the non-reproductive system, it is easy to be misdiagnosed. High-grade extra uterine endometrial stromal sarcoma (HG-EESS) has the diversity of histological structure and lack of typical endometrial stromal sarcoma tongue-like infiltration or immunophenotype, which is easily misdiagnosed as other mesenchymal tumors. Vimentin and CD10 were positive in tumor cells of EESS, but CD10 was more or less expressed in many uterine mesenchymal tumors and sex cord stromal tumors, which indicated that CD10 was more sensitive but not specific in diagnosis. LG-EESS tumor cells maintain the antigenicity of endometrial stromal cells, most of which express hormone antibodies. However, HG-EESS tumor cells loss of differentiated endometrial stromal cells, resulting in ER and PR were negative. At present, there is no specific immunohistochemical marker in the diagnosis of EESS and gene rearrangement is not 100% positive. Histology is still an important basis for examination in daily diagnosis. Some reports [8, 9] that cyclin D1 is diffuse strongly in HGESS, which can be classified with LGESS.

### *Differential diagnosis*

*Endometrial stromal nodule (ESN):* ESN is a benign tumor and well-circumscribed that is usually located in the myometrium (submucosal or intramural), but may also involve the endometrium, protruding into the uterine cavity as a polypoid mass. Microscopically, the histologic features of ESN and LGESS are very similar. ESN has an expansile, but noninfiltrative border that often compresses the surrounding myometrium and endometrium. However, focal finger-like extending into the myometrium can be seen, but should not exceed 3 in number or 3 mm in length. Tumors that exceed this or have lymphatic or vascular invasion should be classified as ESS [10-12]. ESN is typically cellular and composed of small, uniform, round to oval, basophilic nuclei with finely granular chromatin that resemble normal proliferative-phase endometrium. The mitotic activity is usually low.

*Highly cellular leiomyoma:* The cells in highly cellular leiomyoma tend to be slightly larger,

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rod-shaped or cigar-like and have abundant eosinophilic cytoplasm especially at the periphery of the tumor, and there is usually at least a focal rich cell area and the typical bundle area migration that can be appreciated. In addition, highly cellular leiomyomas usually contain thick-walled vessels, scattered mast cells [13]. There are irregular extension between the tumor cells that are adjacent to the myometrium, but have no invasive growth and necrosis. H-caldesmon was positive and CD10 was negative in highly cellular leiomyoma.

*Leiomyosarcoma:* Leiomyosarcoma is a high-grade malignant neoplasm which can mimic HGESS and is characterized mainly by pleomorphic spindle cells in a fascicular growth pattern. A panel of immunohistochemical markers combined with the morphology can be particularly helpful for diagnosis. Positive staining for CD10 without desmin or H-caldesmon staining supports endometrial stromal differentiation, otherwise supports smooth muscle differentiation. Molecular studies that demonstrate a characteristic gene fusion of endometrial stromal tumors may also assist in the differential diagnosis.

*Perivascular epithelioid cell tumor (PEComa):* PEComa can occur in the uterus and consists of epithelioid and spindled cells with moderate to abundant eosinophilic or clear cytoplasm. They are distributed around the blood vessels and rarely infiltrate the myometrium [14]. Immunohistochemically, PEComa is positive for HMB45 and smooth muscle markers, and is negative for CD10.

*Uterine tumor resembling ovarian sex cord tumor (UTROSCT):* UTROSCT is a rare tumor and characterized morphologically by sex cord-like elements that resemble epithelial cells arranged in cords, tubules, or sheets. Although ESN and LGESS may have sex cord-like differentiation that demonstrate varying degrees of inhibin, Calretinin and CD99 expression [15], the endometrial stromal element is the main component. UTROSCT lacks the vascular pattern, and does not exhibit endometrial stromal differentiation.

### *Treatment and prognosis*

Endometrial stromal tumors are a genetically heterogeneous group of tumors that harbor

recurrent chromosomal translocations, producing specific gene rearrangements. The JAZF1-SUZ12 (formerly JAZF1-JJAZ1) fusion identifies a large proportion of ESN and LGESS and recent discovery of a subset of ESS with a unique YWHAE-FAM22 gene rearrangement has redefined and renewed support for the category of HGESS, with distinct morphologic features and a prognosis intermediate between LGESS and UUS. They have different FIGO stage and clinical biological behavior, which is of great significance to the prognosis and treatment. Some scholars [8] have suggested that gene rearrangement is helpful for diagnosis, but not all of the genes have a positive rearrangement. At present, total hysterectomy and double attachment resection is widely used. But for young patients whether to retain the ovary is controversial. Some studies suggest that preserving ovarian or not doesn't affect tumor recurrence [16]. Some scholars believe that with the lesion less than 3 cm we can retain the ovarian [17]. However, most scholars believe that the tumor recurrence rate was higher in those who retain ovarian than in those who do not [18]. In addition, whether to performed pelvic lymph node dissection is also controversial. There is little possibility of lymph node metastasis in LGESS, and lymph node dissection makes no difference in the 5-year survival rate. However, some scholars believe that lymph nodes should be removed [19]. The clinical manifestations of LGESS are indolent and slow in growth. Pelvic recurrence may occur in 1/3 cases, however, the patient can still survive for a long time. Fourteen cases received progestogen therapy, chemotherapy or radiotherapy. Two cases of HGESS died from multiple organ and lymph node metastasis 2 years after operation. Three cases relapsed after 4 years, and were followed up for 2 years after re-operation and radiotherapy. No recurrence was observed in the remaining 9 cases.

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### **Disclosure of conflict of interest**

None.

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**Address correspondence to:** Gaimin Tan, Anyang Tumor Hospital, Anyang, Henan, China. E-mail: tgm\_5-21@163.com

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