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Cytological-Pathologic Correlation

# Retroperitoneal low grade endometrial stromal sarcoma with florid endometrioid glandular differentiation: Cytologic-histologic correlation and differential diagnosis

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ABSTRACT

Low grade endometrial stromal sarcoma (LGESS) is a rare neoplasm that typically arises in the uterine corpus and accounts for less than 1% of uterine sarcomas. Infrequently, extra-uterine LGESS can occur. Histologically, LGESS is characterized by a monotonous population of cells that resemble the proliferative phase of endometrial stroma and in their classic form they exhibit tongue-like growth pattern of infiltration and/or lymphovascular invasion. Infrequently LGESS can demonstrate various morphologic differentiation patterns, including endometrioid-type glands. We report the first fine needle aspiration (FNA) case of a periduodenal mass that was incidentally discovered on Computed Tomography (CT) scan of a 60-year-old female. The cytomorphologic and histologic findings and the immunohistochemical staining were consistent with a LGESS with endometrioid glandular differentiation. We are presenting the correlation between the cytologic, radiologic and pathologic features.

## 1. Introduction

Glandular differentiation in low grade endometrial stromal sarcoma (LGESS) is not common. There are only a few cases that have been described in the literature. This extremely rare gynecologic malignancy is thought to represent the previously designated “aggressive endometriosis” [1]. The cytomorphology of this extremely rare entity has not been described previously. We report the first fine needele aspiration (FNA) and the consequential surgical resection morphology of a case of LGESS with florid endometrioid glandular differentiation (GD). The cytomorphologic, histologic and molecular features, along with differential diagnosis of this rare entity will be discussed.

## 2. Case report

A 60-year-old female G3P3 presented to her primary care physician with severe right flank pain, urinary frequency and urgency. There were no symptoms of fever, nausea or vomiting. Urine analysis and culture were unremarkable. She had past surgical history of hysterectomy and bilateral salpingo-oophorectomy secondary to fibroids and menorrhagia, and bilateral tubal ligation, fifteen years and twenty-seven years earlier, respectively. In addition, her past medical history was significant for hypertension, degenerative disc disease, osteoarthritis, diabetes type II and bilateral cataracts. The patient is thought to have a urinary tract infection, pyelonephritis or a kidney stone. She was prescribed analgesics and was transferred to the emergency department where a CT scan was ordered to check for possible kidney stone. The CT failed to reveal any urolithiasis or hydronephrosis; however, it was significant for a 4.5 × 2.8 × 2.7 cm oval-shaped retroperitoneal mass contiguous with the 3rd portion of the duodenum and abutting the inferior vena cava (Fig. 1A). Retroperitoneal lymphadenopathy was also noted. Based on location and radiologic picture the differential diagnosis included a neoplastic process favoring an exophytic gastrointestinal stromal tumor (GIST), and less likely an infection, an enlarged lymph node or lymphoma. An endoscopic ultrasound (EUS) was performed and showed a hypoechoic mass surrounded by a feeding vessel from the outside wall of the duodenum, with a cystic structure in the middle of the mass (Fig. 1B). An EUS-FNA was performed.

### 2.1. Cytopathologic findings

FNA of the mass showed a hypercellular proliferation of monotonous plump spindled cells with moderate amount of cytoplasm and uniformly-sized oval nuclei that contained conspicuous nucleoli (Fig. 2A). A single layer of columnar epithelium overlying the spindle

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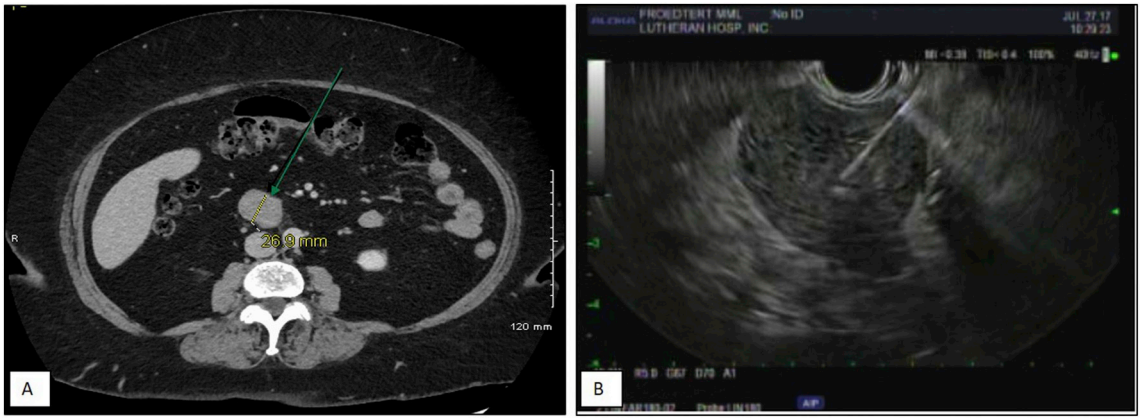


**Fig. 1.** A, CT scan showing oval-shaped retroperitoneal mass (green arrow) contiguous with the 3rd portion of the duodenum and abuting the inferior vena cava. B, Echo-endosonographic image from a linear endoscopic ultrasound showing a hypoechoic mass undergoing fine-needle aspiration. The needle can be seen passing into the mass during collection of cells for rapid on-site examination. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

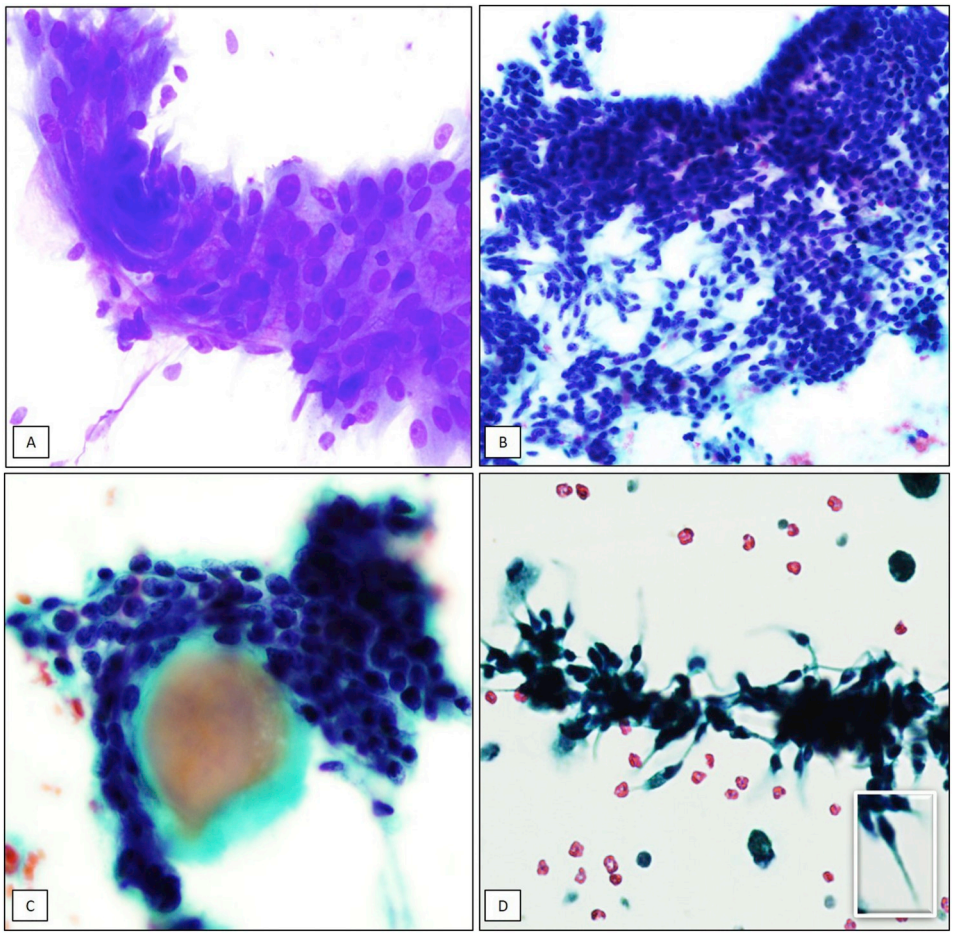


**Fig. 2.** Fine-needle aspiration of LGESS with GD: A, Relatively bland tumor cells clustering around a vascular core (Diff-Quik, original magnification ×200). B, Cells with minimal nuclear atypia forming a flat sheet of spindle cells, occasional scattered epithelioid-appearing cells and an overlying layer of columnar cells. (Papanicolaou, original magnification ×200). C, Two-tone thick material surrounded by round to oval epithelial cells. (Papanicolaou, original magnification ×400). D, Spindled cells "comet cells, inset" surrounding a delicate blood vessel (Papanicolaou, original magnification ×200).

cells was appreciated on the Papanicolaou (PAP)-stained smear (Fig. 2B) and the cell block (Fig. 3). The epithelium appeared to be intimately associated with the stromal cells. Occasional fragments of epithelium in papillary-like arrangements were seen. Thick two-tone mucoid material surrounded by cuboidal cells was appreciated on the PAP-stained smear (Fig. 2C). On air-dried Diff-Quik and alcohol-fixed PAP stained smears, the spindle cells occasionally clustered around vascular core (Fig. 2A,D). Another feature that we found in our case and is commonly seen on ESS was the so called "comet cells" (Fig. 2D inset). Comet cells are spindle-shaped cells with eccentric nuclei and cytoplasmic tapering away from the nucleus. However; they are not specific as they can be seen in other neoplasms. No high-grade epithelial atypia was seen.

Immunohistochemical stains were performed on the cell block preparation (Fig. 3). The neoplastic spindle cells stained positive with CD34 and CD10, and were negative for CK7, CD117(C-KIT), S100, and DOG1. Cytokeratin CK7 highlighted the columnar epithelium overlying the spindle cell proliferation. Immunostains for Estrogen Receptor (ER) and Progesterone Receptor (PR) proteins showed nuclear positivity in the stromal cells as well as in the epithelium. The proliferation index

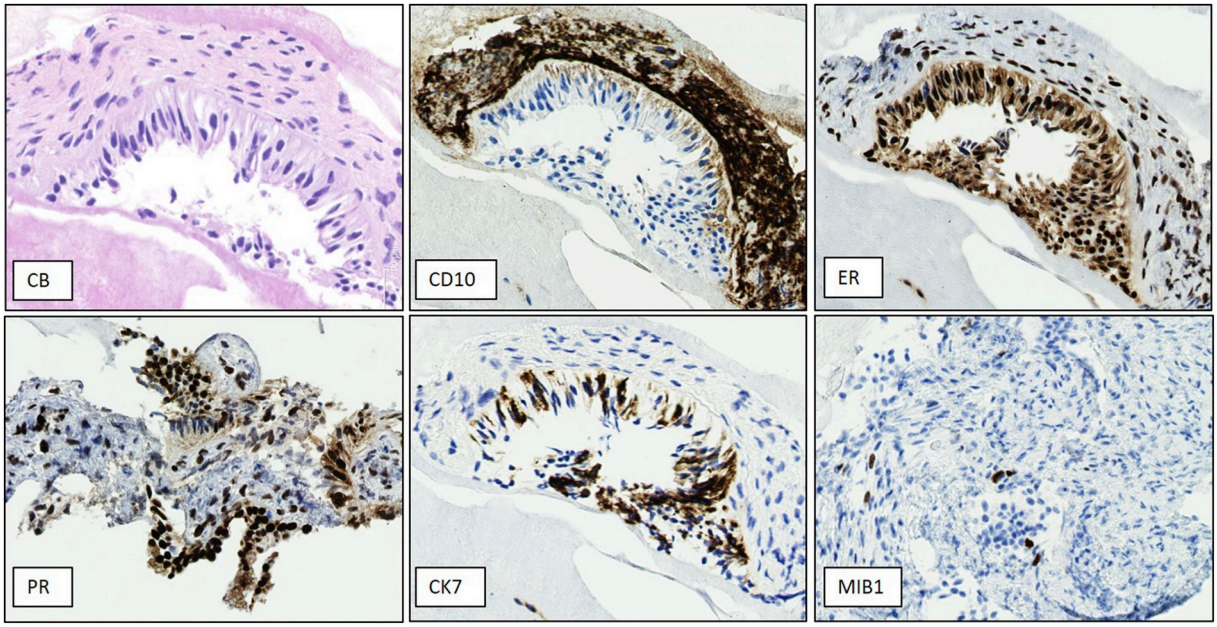


**Fig. 3.** Cell block (CB) showing a sheet of spindle cells with an overlying layer of columnar epithelium giving the biphasic morphology of the tumor. Overlying columnar epithelium was staining positive for CD10, ER and PR and negative for cytokeratin CK7 while the spindle cells were positive for CD10, ER, PR and CK7. Proliferating index MIB-1 showed 1% activity.

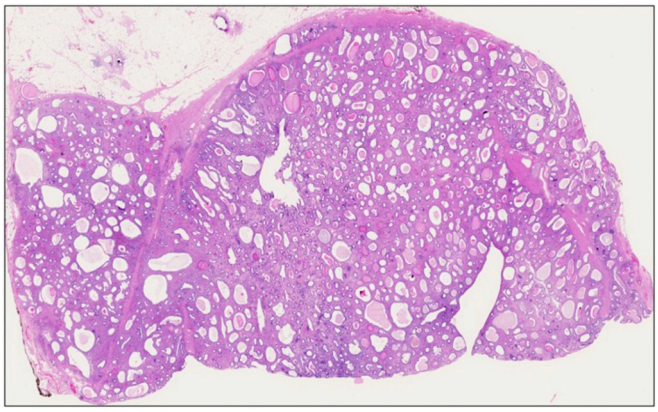

**Fig. 4.** Whole mount slide of LGESS with glandular differentiation; note the involvement of the surrounding adipose tissue (upper left) with LGESS glands.

evaluated by MIB-1 immunostain was approximately 1% in the spindle cell areas.

### 2.2. Histopathologic findings

The retroperitoneal mass was then resected. Hematoxylin and eosin (H&E) stained slides showed a bland-appearing biphasic neoplastic proliferation (epithelial and mesenchymal) composed of dilated glandular structures surrounded by a bland spindle cell stroma. Similar benign-appearing glands were also present in the surrounding adipose tissue (Fig. 4) and in one peritumoral lymph node (Fig. 5A). The glands were lined by ciliated columnar epithelium devoid of cytologic atypia (Fig. 5B). The neoplasm was highly vascular with thin-walled blood vessels spread throughout the tumor. Immunohistochemical stains showed positivity of the glandular structures for CK7, ER/PR and PAX8, and positive staining of the spindle cells in the stroma for CD10, WT1 and ER/PR. Stains for CK20, desmin, CDX2 and villin were negative in the glandular and stromal elements.

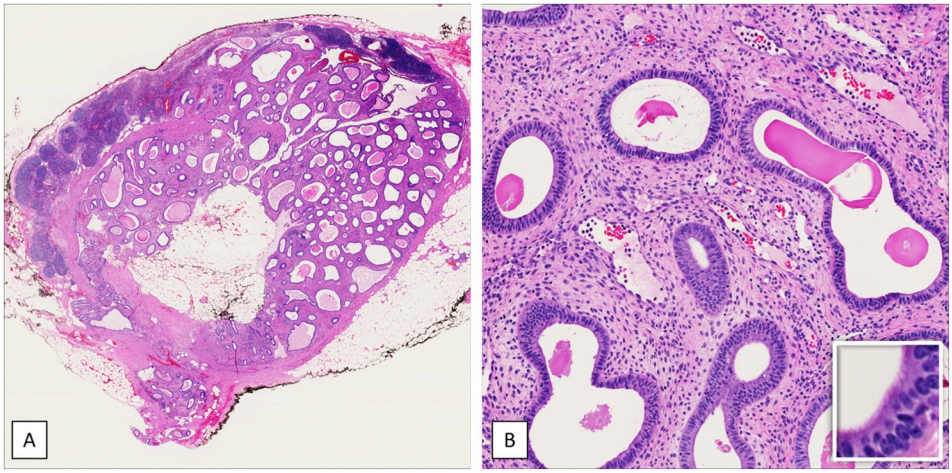


**Fig. 5.** A, Lymph node involvement by LGESS with glandular differentiation. Note the upper normal lymphoid follicles. B, Medium power (original magnification ×100) displaying the florid glandular component surrounded by cuboidal to columnar epithelium and filled with thick eosinophilic material. Note the spindle cell proliferation accompanied by a prominent vasculature that is characteristic of ESS. Inset: Ciliated epithelium (original magnification ×400).

## 3. Discussion

World Health Organization (WHO) 2014 classified ESS into 3 categories: LGESS, high-grade ESS, and undifferentiated uterine sarcoma [2]. Endometrial stromal sarcomas represent approximately 1% of all uterine malignancies and 16% of uterine malignant mesenchymal neoplasms [3]. ESS exhibits a wide variety of morphologic characteristics. This wide assortment of morphology can impose a diagnostic difficulty on fine needle aspiration cytology and on the histologic resection specimen. ESS can show any of the following morphologies: smooth muscle differentiation [4], fibro-myxoid changes [5-7], sex cord-like differentiation [8,9], endometrioid-type glands [4,10], skeletal muscle differentiation and rhabdoid changes [11], clear cell changes [12] and adipocytic differentiation [13].

We have described the first FNA of a case of LGESS with endometrial glandular differentiation which is an extremely rare entity. The glands in the LGESS are usually scarce and focal. In our case the glandular component was present throughout the entire neoplasm which resulted in significant diagnostic difficulty on the fine needle aspiration and the resection specimen. In the uterine corpus where most of the ESSs are seen, the diagnosis is less difficult; especially when we see the conventional type of ESS. Those tumors in their classic form within the uterine corpus demonstrate an infiltrative growth into the myometrium or the lymphovascular spaces. They resemble stromal cells of proliferative-phase endometrium and may exhibit cystic changes, hemorrhage and contain foamy histiocytes. However, extrauterine ESS is uncommon and can be very challenging to diagnose. The peri-duodenal location of LGESS with glandular differentiation has not been reported previously. We report a diagnostically challenging case of periduodenal LGESS with florid endometrioid glands. The radiology of our case favored GIST based on the location. The entities that should be considered in the differential diagnosis diverge with the type and location of ESS. At the benign end of spectrum, the differential diagnosis of extrauterine ESS with florid glands includes endometriosis and endosalpingiosis. In the presence of malignant features, the differential may include metastatic adenosarcoma or carcinosarcoma.

In our case the aspirate smear showed biphasic pattern of monotonous plump spindle cells with an overlying single layer of cuboidal to columnar epithelium. This could be interpreted as mucinous cystic neoplasm (MCN) with ovarian like stroma because of its proximity to the pancreas and particularly if there is thick mucin-like material in the background which was seen occasionally in our case. The aspirates of MCN usually reveal clusters and honeycomb sheets of relatively bland mucin-containing columnar cells present in a background of abundant mucin. The immunoprofile of MCN can mimic that of ESS as the stroma of both can stain for CD10, ER, PR and WT-1. In these cases, clinical and radiologic correlation is critical. MCNs are most often found in the body and tail of the pancreas as unilocular or multilocular cystic masses filled with thick mucoid material [14]. Another consideration is endometriosis (Fig. 6A) which is very commonly seen in association with extrauterine ESS [15] as it has been hypothesized that ESS is derived from endometrial stroma [16-18]. Unequivocal endometriosis was not identified in our case. Additionally, endometriosis by itself can mimic LGESS with glandular differentiation. The former can show the biphasic pattern on FNA and will display the same immunoprofile as in the latter. Endometriosis is less likely to form a well-defined mass and the presence of stroma admixed with hemosiderin laden macrophages in one third of these cases can favor the diagnosis of endometriosis. However, it can be indistinguishable, and caution should be taken as many cases of the ESS with glands were misdiagnosed initially as endometriosis which delayed the diagnosis and the initiation of the treatment [4]. Therefore, the correlation between cytologic findings and radiologic findings is recommended before one diagnosis can be favored over the other. Endosalpingiosis is usually an incidental finding with small glands lined by ciliated tubal-type epithelial cells. The glandular component of our case showed lining of ciliated columnar epithelium; however, the presence of endometrial-type stroma excluded the diagnosis of endosalpingiosis. Psammoma bodies can also be seen on cytology specimens of endosalpingiosis [19].

Initially, we also considered in our case the more remote possibility of a metastasis from an adenosarcoma of the female genital tract. Our patient had hysterectomy with bilateral salpingo-oophorectomy > 15 years ago and the histological examination was performed at a different institution. According to the patient's record, this was done due to uterine fibroids and dysmenorrhea; however, the original surgical specimen for this procedure couldn't be retrieved to confirm the diagnosis and exclude a primary in the uterine corpus. On the low power examination of H&E slides, adenosarcoma will display papillary fronds of cellular stroma projecting from surface of tumor and imparting a phyllodes tumor-like appearance (Fig. 6B). Spindled stromal cells often condense in a concentric layer around the glands known as periglandular cuffing [20]. Carcinosarcoma is at the malignant end spectrum with a biphasic pattern of neoplasm composed of high-grade carcinomatous and sarcomatous elements and typically has an intimate admixture of high-grade epithelium and mesenchyme. The epithelial component is most often endometrioid. The high degree of atypia involving both components will favor the diagnosis of carcinosarcoma over ESS or adenosarcoma.

On the basis of morphological similarity of ESS to the stroma of the proliferative phase endometrium, Norris and Taylor in 1966 [21] were

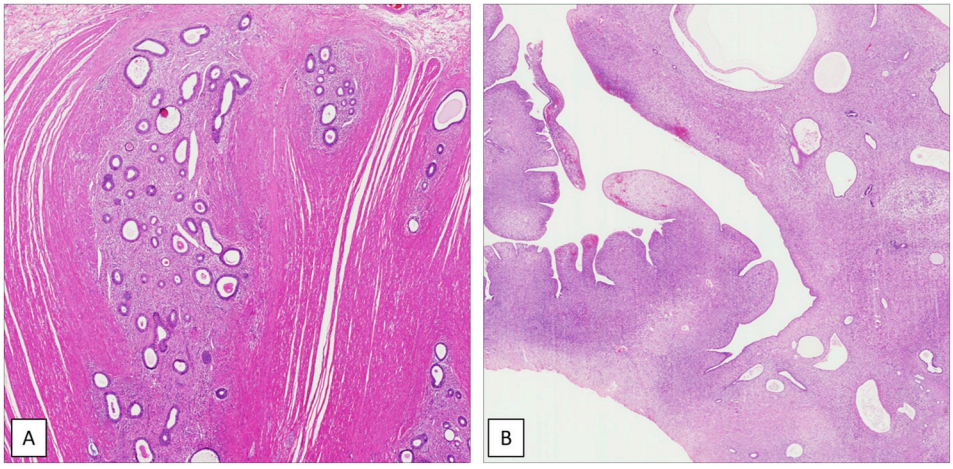


**Fig. 6.** A, Colon resection shows characteristic features of endometriosis, with endometrioid glands surrounded by endometrial stroma (hematoxylin and eosin stain, original magnification ×100). B, Adenosarcoma with phyllodes-like appearance, cystic dilation and periglandular cuffing.

able to classify ESS into 2 categories. Those with < 10 mitoses/10 HPF were called low grade and those with > 10 mitoses/10 HPF were called high grade. Afterwards, it has been argued that the number of mitoses within ESSs is largely irrelevant to outcome [22,23] and since then, different subsequent classifications were developed [24]. The morphologic and genetic heterogeneity of ESSs, and the diagnostic complexity made it very challenging to depend solely on histologic evaluation. The WHO reintroduced ESSs into the 2014 edition with a new classification based on molecular alterations that are recognized in the ESSs. The most commonly encountered translocation in LGESS is t (7;17)(p21;q15) with subsequent JAZF1/SUZ12(JJAZ1) fusion which is present in more than half of the ESSs [25,26].

In summary this report provides the first evaluation of the fine needle aspiration cytology of extrauterine LGESS with endometrioid glandular differentiation and the first to present as retroperitoneal mass. ESS is easy to diagnose when present in their classic morphology in the uterine corpus and can be very challenging in extrauterine locations. These tumors as in our case are usually incidentally discovered masses with indolent biological behavior and tend to recur late. Cognizance of this entity and awareness of its locations and variable morphologic pattern are critical to make an accurate diagnosis. Excluding a primary in the uterine corpus is as well important if feasible.

## Disclosure

No relevant financial disclosures.

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