Unusual Presentations of Gynecologic Tumors
Primary, Extrauterine, Low-Grade Endometrioid Stromal Sarcoma
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Context.—Low-grade endometrial stromal sarcomas, when uterine in location, are relatively easy to diagnose because of characteristic morphology and patterns of myometrial invasion. However, when they occur at extrauterine sites, they fall under the broad umbrella of small round blue cell tumors, making diagnosis challenging, especially when they have variant morphologic features and lack the characteristic pattern of invasion.

Objectives.—To provide an insight into the sites of occurrence of low-grade endometrioid stromal sarcomas, the variant morphologic patterns, clues to diagnosis, and the usefulness of immunohistochemistry as an aid to facilitate correct diagnosis. The outcome of these tumors, in comparison with their uterine counterpart, is also discussed.

Data Sources.—Existing peer-reviewed literature was reviewed.

Conclusions.—Low-grade endometrioid stromal sarcoma is an uncommon neoplasm that can be misdiagnosed because of its rarity, unusual location, and presence of numerous variant histologic patterns that mimic other tumors. Knowledge of those features; consideration of this tumor in the differential diagnosis of small, round blue cell tumors at any location in a woman; and an appropriate use of immunohistochemistry can help facilitate the diagnosis.

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Low-grade endometrial stromal sarcoma is a rare uterine tumor and accounts for 0.2% of malignancies of the gynecologic tract. Primary, extrauterine, low-grade endometrioid stromal sarcomas (LGEESSs) are even rarer tumors that arise de novo at extrauterine sites, with no uterine involvement.1 When uterine in location, endometrial stromal sarcomas (ESSs) are easy to diagnose because of their characteristic histology and patterns of invasion. However, when they occur at extrauterine sites, they produce nongynecologic signs and symptoms. In addition, the presence of variable histologic features and lack of a unique immunohistochemical profile can pose a diagnostic dilemma and lead to inaccurate diagnoses. Association of LGEESS with endometriosis is seen in about two-thirds of cases, suggesting that most of these tumors originate by malignant transformation of the stromal component of endometriosis. Literature on this entity is limited to 2 large case series and several case reports.

SITES OF INVOLVEMENT AND CLINICAL PRESENTATION
These tumors occur throughout a wide age range, with a mean age in the sixth decade.2,3 The clinical signs and symptoms depend on the site of involvement. The common sites of involvement reported are typically sites in which endometriosis occurs and include abdominopelvic sites, specifically the peritoneal surfaces, bowel wall, ovaries, pelvis, vagina, urinary bladder, retroperitoneum, lymph nodes, and fallopian tubes2,3 (Figure 1, A and B). Thus, the common presentations usually include abdominal/pelvic mass and pain, abnormal vaginal bleeding, gastrointestinal symptoms such as vomiting, constipation, bleeding, and small bowel obstruction, and urinary symptoms, such as hematuria, urgency, frequency, and incontinence.2–4 Several unusual sites of presentation for LGEESS described in the literature include dysphagia and hoarseness with laryngeal involvement, pelvic fracture from a primary bone LGEESS, radiculopathy secondary to a vertebral body tumor, elevated serum creatinine from a periureteral tumor, and motor nerve deficit from sciatic nerve involvement.2,5 In some cases with unusual locations, other abdominopelvic sites of involvement have been discovered on subsequent imaging and workup; however, the unexpected location led to significant diagnostic difficulties at initial presentation. Some tumors were also discovered incidentally during workup of an unrelated illness.2,6–8 In the largest series on this entity, only 50% of the tumors were accurately diagnosed initially.2

PATHOLOGIC FEATURES
The tumor size ranges from 1 to 25 cm, with a mean of 8–11 cm.2,9 Most are solid, grossly circumscribed, and are described as tan-yellow and multinodular, although cystic...
areas are not infrequent, especially if associated with endometriosis. A typical ESS pattern consists of monotonous, oval to fusiform cells, with scant cytoplasm, resembling stromal cells of proliferative endometrium, interspersed with small spiral, arteriole-like vessels. Cytologic atypia is minimal in LGEESS. In the uterus, ESS has a characteristic tongue-like pattern of invasion into the myometrium and is frequently associated with lymphatic invasion. This pattern of invasion may be lacking at extraterine sites, where the tumor typically has a multi-nodular appearance. A fibroblast-like stromal pattern is described in more than one-half of LGEESSs and is uncommon in uterine tumors. Other morphologic patterns seen that are not unique to extraterine sites include prominent hyaline plaques, foam cell change, florid glandular differentiation, sex cord elements, and prominent myxoid changes. Smooth muscle differentiation, epithelioid cell changes, and clear cell changes have been reported less frequently. Hemangiopericytoma-like vascular patterns can be seen. These patterns and the extraterine locations result in LGEESS mimicking several other tumors and are a significant source of diagnostic error.

IMMUNOHISTOCHEMISTRY

The LGEESS tumor cells, as in the uterine counterpart, are diffusely and strongly positive for CD10. Estrogen receptors and progesterone receptors are positive in most tumors; progesterone receptor staining by immunohistochemistry is considered a prerequisite to institute hormonal therapy by most clinicians. Wilms tumor 1 (WT1) is positive in many tumors. Areas of smooth muscle differentiation usually show strong and diffuse staining for muscle markers, such as desmin and h-caldesmon. Smooth muscle actin is usually positive in conventional LGEESSs as well as in areas with smooth muscle differentiation. Inhibin, calretinin, Melan-A, and CD99 are usually positive in areas with sex cord–like differentiation but are absent in conventional areas. Focal expression of keratin (AE1/AE3) may also be seen.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies depending on the location of the tumor as well as the variant histologic patterns. Metastatic endometrial stromal sarcoma of uterine origin should always be excluded.

Based on Location

Ovary.—In cases of LGEESS involving the ovary, the differential diagnosis is mainly with sex cord stromal tumors and includes adult granulosa cell tumor, fibroma, thecoma, and fibrosarcoma. Nuclear grooves, monotonous low-grade cells, and diffuse and pseudopapillary patterns can be seen in ESS and can potentially be a pitfall in the diagnosis of LGEESS of the ovary versus adult granulosa cell tumor. Areas of endometriosis as well as extraovarian spread favor LGEESS, whereas hormonal manifestations favor adult granulosa cell tumor. Fibroma-like areas of LGEESS may mimic an ovarian fibroma. Hyaline plaques, frequently noted in ESS, are also seen in thecomas. The characteristic vascular pattern of ESS is an important diagnostic clue and should be looked for carefully. An immunohistochemical panel of CD10, inhibin, calretinin, and CD56 may be useful.
in distinguishing ESS from sex cord stromal tumor, keeping in mind that markers of sex cord–like differentiation (inhibin and calretinin) may be strongly positive in sex cord–like areas of ESS. CD10 tends to be positive in sex cord stromal tumor but is usually patchy in contrast to ESS. CD56 is usually positive in sex cord stromal tumor but negative in ESS.

**Abdominopelvic Cavity.**—In the abdominal cavity, gastrointestinal stromal tumor is an important differential study. Morphologically, the tumors are usually distinct, with

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**Figure 2.** Low-grade endometrioid stromal sarcoma with fibroma-like stromal pattern (A), abundant hyaline plaques (B), foam cell change in the tumor cells (C), glandular differentiation within the tumor (D), sex cord differentiation (E), and prominent myxoid change within the tumor (F) (hematoxylin-eosin, original magnifications ×100 [A, B, D, and E] and ×200 [C and F]).
gastrointestinal stromal tumors showing nuclear palisading and fascicular arrangement, in contrast to the plump, round to oval cells of ESS. Gastrointestinal stromal tumor can be excluded with the combined use of c-Kit, CD34, and DOG1 stains. Smooth muscle tumors are frequently in the differential diagnosis of ESS, when uterine in location, and may occasionally pose challenges in the extrauterine pelvic location. Significant overlap in staining for CD10 and desmin can occur in ESS and smooth muscle tumors; hence, a panel that includes additional smooth muscle

Figure 3. Low-grade endometrioid stromal sarcoma with smooth muscle differentiation (A), starburst pattern of collagen seen frequently with smooth muscle differentiation (B), pseudopapillary pattern (C), angiomatous pattern mimicking vascular tumors (D), epithelioid cells (E), and extensive clear cell change with slit-like vessels (F) (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B through F]).
markers, such as h-caldesmon, calponin, or SMMS-1, which are usually negative in ESS, should be used.

**Soft Tissue.**—Spindle cell morphology, bland cytology, and abundant collagen result in the differential diagnosis of solitary fibrous tumor (SFT) and synovial sarcoma. Endometrial stromal sarcoma can focally show staghornlike vessels seen in SFT; however, that finding is focal in LGESS, and the typical, small, round arterioles help make the diagnosis. Estrogen receptor is usually negative in SFT and synovial sarcoma. Progesterone receptor staining, albeit patchy, has been reported in 50% of SFTs. CD34 is positive in SFT and negative in the other 2 entities. TLE1 is a relatively specific immunohistochemical marker of synovial sarcoma as is molecular analysis for t(X;18) translocation.

**Bladder.**—In most cases, bladder involvement is a part of multiple organ involvement and does not suggest a primary bladder tumor. In cases presenting with urinary symptoms and showing a bladder mass, the differential diagnosis includes SFT, synovial sarcoma, carcinoid, primitive neuroectodermal tumor, and large, nested variants of urothelial carcinoma. The first 2 diagnostic differentials were discussed in the previous paragraph. Carcinoid tumors and ESS have been reported to have immunohistochemical overlap with ESS staining for CD56 and synaptophysin and carcinoid tumors that variably stain with estrogen receptor, progesterone receptor, or CD10. However, morphology and diffuse estrogen receptor, progesterone receptor, and CD10 staining in LGESS should help distinguish the 2 entities. CD99, seen in primitive neuroectodermal tumors, is usually negative in LGESS. The wormlike pattern of invasion seen in LGESS is similar to that of infiltration seen in the large, nested variant of urothelial carcinoma. Distinguishing features between these entities in the bladder that favor large, nested variants of urothelial carcinoma include a desmoplastic response (typically not seen in ESS), cells with more abundant cytoplasm and distinct cell borders, and an in situ lesion, when present. GATA3 and thrombomodulin are positive in large, nested variants of urothelial carcinoma and negative in ESS.

**Based on Morphologic Pattern**

Presence of variant morphologic patterns within LGESS can raise several diagnostic possibilities. The presence of fibroma-like stroma or hyaline plaques may impart the appearance of fibroma or thcoma. Smooth muscle differentiation raises the possibility of smooth muscle tumors or mixed tumors. Presence of glandular differentiation may necessitate exclusion of florid endometriosis and adenosarcoma. Presence of sex cord differentiation requires distinction from granulosa cell tumors. Hemangioepithelyoma-like vascular pattern can lead to the mistaken diagnosis of SFT. Careful attention to histologic features and recognizing areas of typical ESS that are almost always present, along with an appropriate immunohistochemistry panel (elaborated previously), will help clinch the diagnosis. It is important to keep LGESS in the differential diagnosis of small, round blue cell tumors in women.

**GENETIC PROFILE**

Cytogenetic studies of endometrial stromal tumors have recognized several reciprocal translocations. Similar to uterine ESS, LGESSs have been reported to harbor fusion of JAZF1-SUZ12 (JAZ1) genes as a result of t(7;17)(p15;q21), albeit with a lesser frequency, probably because of fewer numbers of cases being tested. The JAZF1-SUZ12 fusion has been identified in tumors with conventional morphology and with smooth muscle differentiation but less commonly in the other morphologic variants. PHF1 gene rearrangements resulting from t(6;10)(p21;p11) and t(6;7)(p21;p15), with fusion of EPC1-PHF1 and JAZF1-PHF1, respectively, are preferentially seen in endometrial stromal tumors with sex cord–like differentiation. The recently described high-grade endometrial stromal sarcoma with distinct morphology and characteristic YWHAE-FAM22 (Nutm2) genetic rearrangement resulting from t(10;17)(q22;p13) has not been reported at extraterine sites, but that translocation has been described in fibromyxoid variant of uterine, low-grade ESS.

**PATHOGENESIS AND RISK FACTORS**

An association with endometriosis has been reported in 60% to 69% of cases. This suggests that most of these tumors originate from the ectopic endometrial stroma of endometriosis. An association with hormone replacement therapy was noted in postmenopausal patients with LGESS.

**TREATMENT, PROGNOSIS, AND OUTCOME**

Treatment guidelines are based on those for uterine ESS. Cytoreductive surgery is the first line of treatment in these patients with or without adjuvant hormonal therapy. Radiation and chemotherapy are usually reserved for refractory or recurrent disease.

In uterine ESS, stage appears to be the most important prognostic factor. The 5-year disease-specific survival for stages I and II is 90% and drops to 50% for stages III and IV.

There are conflicting data regarding the behavior of primary LGESS. Chang et al reported primary LGESS to behave similar to high-stage uterine ESS. Masand et al found that LGESS had a clinically indolent behavior, similar to low-stage uterine ESS, with a propensity to develop recurrences. Most other case reports and series also suggest a more-indolent behavior for these tumors.

Clinical and histologic features, such as tumor size, tumor location, mitotoc index, and vascular invasion, do not appear to correlate with clinical outcome. In LGESS, single versus multiple sites of extraterine disease also do not appear to influence outcome. The only histologic feature that suggests a worse prognosis is synchronous or metachronous development of high-grade cytologic features (dedifferentiation). However, literature on dedifferentiated tumors arising in LGESS is sparse.

**SUMMARY**

Primary low-grade endometrioid stromal sarcomas occur at extraterine sites, and when they do so, can pose problems in diagnosis because of unexpected location, nongynecologic signs and symptoms, presence of variant histologic patterns, and lack of a unique immunohistochemical profile. Many of these tumors arise in association with endometriosis, suggesting an origin from ectopic endometrial stroma. Awareness of presentation at extraterine locations and attention to histologic features are important in making an accurate diagnosis. Metastasis from a uterine primary must be excluded. Primary, extraterine, low-grade endometrioid stromal sarcomas
appear to be indolent tumors with a propensity for late recurrences.

References