Editorial

Diagnostic challenges and considerations of low-grade endometrial stromal sarcoma (LGESS) outside the female genital tract

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Comment on: Zhang Y, Wei Z, Yan J, *et al.* Endometrial stromal sarcoma metastatic to the inferior vena cava: a case report and literature review. Transl Cancer Res 2022;11:3421-5.

Submitted Aug 22, 2022. Accepted for publication Sep 09, 2022.
doi: 10.21037/tcr-22-2098
View this article at: https://dx.doi.org/10.21037/tcr-22-2098

Low-grade endometrial stromal sarcoma (LGESS) is a rare low grade sarcoma of endometrial stromal origin that occurs most often in the uterine corpus and cervix, with the ovary being the most common extrauterine location (1). Primary LGESS outside the female genital tract is exceedingly rare, and most cases are associated with endometriosis (2). In addition, although generally following an indolent clinical course, LGESS of the female genital tract can occasionally metastasize to other locations such as the lung, colon, pancreas, and breast, etc. (3-6). The correct diagnosis of LGESS (primary or metastatic) outside the female genital tract is clinically important because LGESS responds to hormone-based therapy, which could provide great benefits to patients (7). However, LGESS outside the female genital tract poses unique diagnostic challenges for several reasons that are briefly discussed below.

First, LGESS can metastasize many years after initial diagnosis (1). Careful inquiry of the potential medical history of uterine or ovarian LGESS is an important first step for a correct diagnosis.

In addition, mesenchymal tumors that are more common in locations outside the female genital tract could show imaging, histological, and immunohistochemical features overlap with LGESS. For example, Zhang *et al.* (8) reported a case of metastatic uterine LGESS involving the inferior vena cava (IVC), which was initially thought to be IVC leiomyomatosis based on imaging studies, mainly because of the tumor location, overlapping imaging features, and incomplete clinical history at the time of presentation. Histopathological examination revealed classic LGESS morphology with small spindle cells admixed with abundant spiral arteriole-like vessels. Although there was a significant overlap in immunoprofiles with leiomyoma [positive smooth muscle actin (SMA), estrogen receptor (ER), progesterone receptor (PR)], a positive CD10 stain combined with morphology and a remote clinical history of uterine LGESS led to the correct conclusion of metastatic LGESS in the IVC (8). Other differential diagnoses of LGESS outside the female genital tract include, but are not limited to, perivascular epithelioid cell neoplasm (PEComa), gastrointestinal stromal tumor (GIST), fibromatosis, and solitary fibrous tumor. An extensive immunostaining panel is crucial for ruling out these possibilities.

Furthermore, it has been well documented that LGESS can have other lineage differentiations, such as smooth muscle, fibroblastic, osteoclast-like, sex-cord, adipocytic, skeletal muscle, focally or extensively (9-13). LGESS resembles these differentiations both morphologically and immunohistochemically, making diagnosis of LGESS difficult in some cases. Adequate sampling of the tumor and a thorough search for areas of classic LGESS morphology are imperative for a correct diagnosis. Molecular testing for frequently occurring fusion genes (most commonly involving *JAZF1* or *PHF1*) may be helpful in difficult cases (14).

LGESS with endometrioid glandular differentiation is a rare variant that causes unique diagnostic difficulties,

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particularly at locations outside the female genital tract (15). The mesenchymal component of this variant exhibits classic LGESS morphology consisting of small bland spindle tumor cells admixed with frequent small arteriole-like vessels with tongue-like infiltrative invasion. However, there are benign endometrioid glands disposed within the spindle cell background. The main differential diagnoses of this LGESS variant in extrauterine locations are adenosarcoma and endometriosis.

Both LGESS with glandular differentiation and adenosarcoma can arise from endometriosis, and are composed of a low-grade sarcomatous component of endometrial stromal origin intermixed with a benign endometrioid glandular component (16). Immunohistochemistry (IHC) studies are therefore not beneficial, and differentiation between the two rests on morphological features and molecular alterations. In LGESS with glandular differentiation, the benign endometrioid glands appear simply "trapped" within the stromal component. On the other hand, peri-glandular stromal condensation (cuffing) and intra-luminal epithelial lined stromal projections (phyllodes tumor-like) are essential diagnostic morphological features for adenosarcoma. Stromal cell atypia and increased mitotic activity are also suggestive of adenosarcoma. A fusion gene involving *JAZF1* or *PHF1* confirms a diagnosis of LGESS (14,17).

Endometriosis, also consists of bland endometrioid glands "trapped" in a background of endometrial stroma. However, in LGESS with endometrioid glandular differentiation, the glands often appear further apart due to the expansile growth of the stromal component. Sometimes, it is impossible to differentiate between the two based on morphology alone, especially in small biopsies, and/or if the endometriosis is gland-poor. It has been proposed that if repeated sampling of a tumor-like mass results in endometriosis-like findings, LGESS with glandular differentiation should be considered (18). Area of conventional LGESS morphology devoid of glandular component, expansile stromal growth, and the presence of lymphovascular invasion with or without a glandular component favor the diagnosis of LGESS with glandular differentiation. Molecular testing may be helpful in confirming the diagnosis in difficult cases.

The correct diagnosis of primary or metastatic LGESS outside the female genital tract is challenging. However, careful clinical history inquiry, adequate sampling, thorough histologic examination in search of classic LGESS morphology, familiarity with the immunoprofile and morphological variations of LGESS, and targeted molecular testing are prudent steps to ensure an accurate diagnosis.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2098/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Niu S. Diagnostic challenges and considerations of low-grade endometrial stromal sarcoma (LGESS) outside the female genital tract. Transl Cancer Res 2022;11(10):3445-3447. doi: 10.21037/tcr-22-2098

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