Case Report

Immunohistochemical Characterization of Endometrial Stromal Sarcomas

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DOI
10.21276/apalm.3566

Article History
Received: 11-04-2025
Revised: 13-07-2025
Accepted: 04-08-2025
Published: 20-08-2025

How to cite this article
Marwah N, Kalyan M, Bhargava S, Singh S. Immunohistochemical Characterization of Endometrial Stromal Sarcomas. Ann Pathol Lab Med. 2025;12(08):C118-C121.

Abstract

Endometrial stromal sarcomas (ESS) are rare uterine mesenchymal tumors with overlapping histological and immunohistochemical features. High-grade ESS (HG-ESS) is typically characterized by high mitotic activity, marked pleomorphism, strong cyclin D1 expression, and negativity for hormone receptors. Accurate diagnosis is critical for appropriate treatment and prognosis. We report a case of a 75-year-old postmenopausal female presenting with abnormal uterine bleeding. Histopathological examination revealed a pleomorphic, highly cellular tumor with elevated mitotic activity (8–10/HPF). Immunohistochemistry showed strong positivity for vimentin, panCK, cyclin D1, ER, and PR. Beta-catenin staining was cytoplasmic and membranous, with no nuclear localization. SMA and MyoD1 were negative. Despite ER/PR positivity and absence of nuclear beta-catenin, the overall findings favored a diagnosis of high-grade endometrial stromal sarcoma. This case highlights the importance of integrating histomorphological features with a comprehensive IHC panel. Strong cyclin D1 expression, high mitotic index, and exclusion of other differential diagnoses supported the diagnosis of HG-ESS, despite conflicting ER/PR and beta-catenin findings.

Keywords: Endometrial stromal sarcoma; high-grade ESS; cyclin D1; immunohistochemistry; beta-catenin; ER/PR; uterine sarcoma

Introduction

One of the most common situations in gynecological pathology that requires the use of immunohistochemistry is the differentiation of different types of malignancy when there are histomorphological overlapping grey areas. This differentiation is important, as it will help to guide the surgeons in their surgical planning and subsequent treatment approach. In order to differentiate the type of malignancy, a panel of immunohistochemical markers are used.

The Uterine leiomyosarcomas (ULMS) as well as endometrial stromal sarcomas (ESS) constitute the majority of uterine mesenchymal tumors [1]. With the growing prevalence of limited sampling procedures that may make it difficult to accurately classify tumors, uterine mesenchymal tumors can occasionally present a diagnostic problem when their morphologic traits overlap. With uterine mesenchymal neoplasms, immunohistochemistry (IHC) may be employed to differentiate between smooth muscle as well as endometrial stromal differentiation. While expression of “muscle-specific actin” (MSA), “desmin,” and “smooth muscle actin” (SMA) has been indicative of smooth muscle tumors, CD10 usually exhibits diffuse, strong staining in endometrial stromal tumors. The profile of immunohistochemistry of the two groups, however, shows divergent findings, which could be problematic for diagnosis if only one marker or a small panel is used. The endometrial stromal tumors frequently provide positive results from Desmin as well as SMA immunostains, while CD10 expression is seen in nearly half of cellular leiomyomas [2].

The WHO 2020 classification divides endometrial stromal tumors into low-grade endometrial stromal sarcomas (LG-ESS), high-grade endometrial stromal sarcomas (HG-ESS), endometrial stromal nodules, as well as undifferentiated uterine sarcoma (UUS) [3]. Progesterone receptor (PR), cyclin D1, Estrogen receptor (ER), CD10, as well as beta-catenin constitute the standard immunomarker panel that pathologists employ. There is a lot of overlap, and distinct entities might react to the same antibodies in various ways. PR, ER, as well as CD10 immunostains are usually negative for high-grade endometrial stromal sarcoma, and over 70% of tumor cell nuclei have diffuse, strong cyclin D1 staining. In contrast, generally, low-grade endometrial stromal sarcoma shows negative or just localized cyclin D1 immunostaining. However, since uterine leiomyosarcomas might exhibit cyclin D1 expression, it is always important to interpret the results in the context of a larger immunopanel [4, 5].

Thus, Endometrial stromal sarcomas (ESS) are rare uterine mesenchymal tumors with overlapping histopathological features that can mimic other gynecologic malignancies. Accurate classification is crucial, as the biological behavior and treatment approach differ markedly among low-grade ESS (LG-ESS), high-grade ESS (HG-ESS), and other uterine sarcomas. While HG-ESS is typically negative for estrogen receptor (ER), progesterone receptor (PR), and CD10, it often shows strong nuclear cyclin D1 expression. In contrast, LG-ESS commonly expresses ER, PR, and CD10 and is usually negative for cyclin D1 [6, 7]. Given this variability, immunohistochemistry (IHC) plays a vital role in resolving diagnostic ambiguity. Here, we report a diagnostically challenging case of HG-ESS showing paradoxical ER/PR positivity and cytoplasmic beta-catenin expression, which underscores the importance of correlating morphology with a full IHC panel.

Case Report

A 75-year-old postmenopausal female presented with abnormal uterine bleeding lasting 15 days. On examination, the vagina was normal, the cervix was hypertrophied, and the uterus was anteverted and of normal size. Transvaginal ultrasonography revealed a thickened endometrium (16.5 mm) with cystic changes suggestive of cystic endometrial hyperplasia.

Endometrial biopsy showed cystically dilated glands and a cellular stroma composed of large pleomorphic tumor cells, arranged in gland-like structures and diffuse sheets. The tumor cells exhibited marked nuclear pleomorphism, hyperchromasia, irregular nuclear membranes, and prominent nucleoli. The mitotic index was elevated (8–10 mitoses per 10 high-power fields) (Figure 1). These histomorphological features raised differential diagnoses of endometrial adenocarcinoma/carcinosarcoma, leiomyosarcoma, and high-grade stromal sarcoma.

IHC analysis revealed that the tumor cells were strongly positive for vimentin, pan-cytokeratin (panCK), cyclin D1 (Figure 2), ER, and PR. Beta-catenin (Figure 3) showed cytoplasmic and membranous staining only, with no nuclear localization. Focal positivity was seen for CD10 and WT1. Tumor cells were negative for SMA and MyoD1, ruling out smooth muscle differentiation. The Ki-67 proliferation index was approximately 50% (Figure 4), confirming high proliferative activity.

Although ER and PR positivity typically suggests LG-ESS, the high-grade cytologic features, diffuse strong cyclin D1 expression, absence of nuclear beta-catenin, and lack of smooth muscle marker expression supported a final diagnosis of high-grade endometrial stromal sarcoma (HG-ESS).

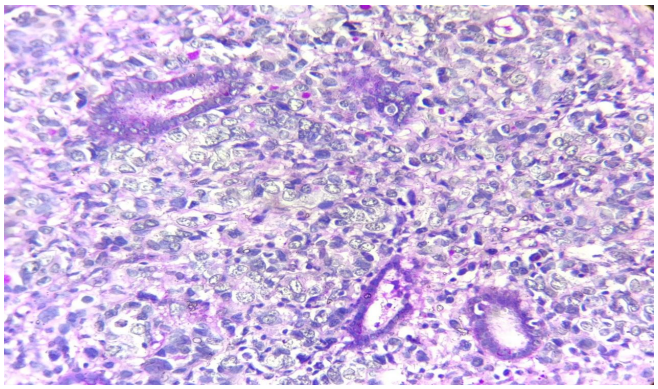

Figure 1: Endometrial tissue showing cystically dilated endometrial glands and cellular stroma containing large pleomorphic cells arranged in the form of glands and diffuse sheets. (H & E; 100x)

Discussion

Diagnosing uterine mesenchymal tumors can be complex due to overlapping morphological and immunohistochemical features. In this case, the differential diagnoses included carcinosarcoma, uterine leiomyosarcoma, low-grade ESS, and HG-ESS.

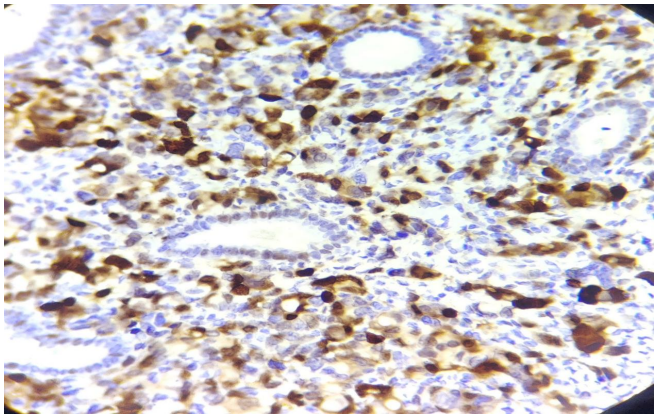

Figure 2: The pleomorphic cells were diffuse strong positive for cyclin D1 [IHC; x400].

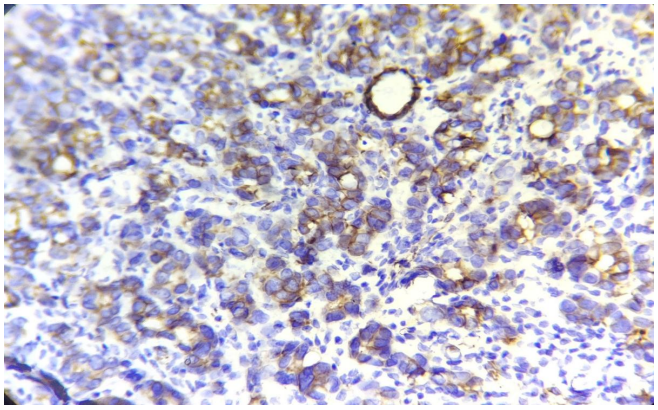

Figure 3: The pleomorphic cells were diffuse membranous and cytoplasmic positive for Beta-catenin [IHC; x400].

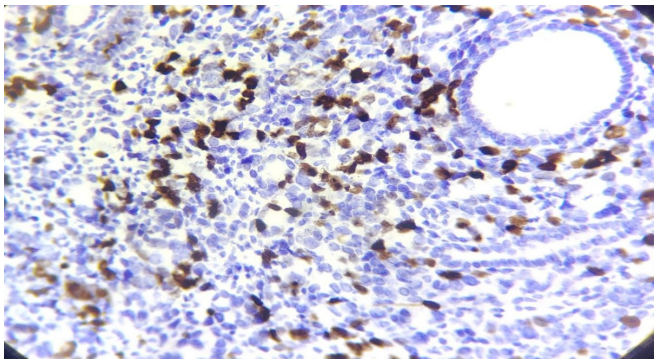

Figure 4: Ki-67 proliferation index $>$ 20%. [IHC; x400].

Carcinosarcoma was initially considered due to the presence of gland-like structures and panCK positivity. However, carcinosarcomas typically display biphasic malignant epithelial and mesenchymal components, which were not observed here. Furthermore, panCK expression in stromal tumors is not uncommon and can represent aberrant expression rather than true epithelial differentiation [6, 7]. The absence of a clearly demarcated carcinomatous component argued against carcinosarcoma.

Leiomyosarcoma was ruled out based on negative SMA and MyoD1, and lack of morphologic features such as fascicular smooth muscle arrangement. In contrast, leiomyosarcomas frequently express smooth muscle markers and show lower cyclin D1 expression [8, 9].

LG-ESS was considered due to the ER/PR positivity. However, LG-ESS usually displays bland cytology, lower mitotic activity, nuclear beta-catenin expression, and minimal pleomorphism [3, 10]. In this case, marked pleomorphism, a high mitotic index, and the absence of nuclear beta-catenin made LG-ESS unlikely.

The most consistent findings supported a diagnosis of HG-ESS included marked nuclear pleomorphism and a high mitotic rate (8–10/HPF), diffuse, strong nuclear cyclin D1 positivity [4, 11], a high Ki-67 index ($\sim$50%), negative SMA/MyoD1, excluding smooth muscle tumors, and focal CD10 positivity in a high-grade tumor setting. Although ER and PR positivity

is unusual in HG-ESS, it is not incompatible. Some cases of HG-ESS have shown ER/PR expression, particularly when they lack classical YWHAE rearrangements or show histologic variability [11, 12]. Similarly, cytoplasmic or membranous beta-catenin staining—as seen in this case—is not indicative of Wnt pathway activation and is non-specific. Only nuclear beta-catenin localization supports a diagnosis of LG-ESS or specific molecular subtypes [3, 10].

Thus, despite the paradoxical ER/PR positivity and lack of nuclear beta-catenin, the overall morphologic and IHC profile supports a diagnosis of HG-ESS. This case highlights the importance of interpreting IHC results in conjunction with morphology and in the context of a full IHC panel.

Conclusion

This case illustrates the diagnostic complexity of uterine mesenchymal tumors and underscores the need for a multimodal approach. While ER and PR positivity and the absence of nuclear beta-catenin might suggest a low-grade neoplasm, these findings must be interpreted cautiously. In this patient, marked nuclear pleomorphism, high mitotic activity, strong cyclin D1 expression, and exclusion of carcinosarcoma and leiomyosarcoma favored the diagnosis of high-grade endometrial stromal sarcoma. The case reinforces that no single immunohistochemical marker is definitive, and diagnostic accuracy relies on the integration of morphology, IHC profiles, and clinical context.

Acknowledgements: The authors would like to express their gratitude to the Department of Pathology, PGIMS Rohtak, for providing the necessary facilities and support in conducting this case study. We also thank the laboratory and technical staff for their assistance with immunohistochemical procedures.

Funding: This study received no external funding.

Competing Interests: No conflict of interest.

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