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*Case Report*

# Pleomorphic high grade endometrial stromal sarcoma with *YWHAE* gene amplification may be a novel variant with poor prognosis

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**Abstract:** Endometrial stromal neoplasms are classified by the World Health Organization (WHO) into endometrial stromal nodule (ESN), low grade (LGESS), high grade (HGESS), and undifferentiated uterine sarcoma (UUS). HGESS is subclassified based on molecular findings, *YWHAE* or *BCOR*. The HGESS with *YWHAE::NUTM2A/B* (alias *YWHAE::FAM22A/B*) fusion usually have relatively monomorphic (as with most fusion-associated malignancies) rounded to epithelioid cells with eosinophilic cytoplasm, vesicular nuclei, nucleoli, and mitotic figures >10/10 HPF. We present a 66-year-old woman with post-menopausal bleeding found to have a heterogeneous solid-cystic uterine mass on CT who underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node dissection. A 15.0×9.0 cm variegated uterine mass with hemorrhage and necrosis was identified. Histologically, the tumor was hypercellular with haphazard fascicles, microcysts, and tongue-like destructive myometrial invasion. Tumor cells exhibited marked pleomorphism and high mitotic activity with atypical mitotic figures. There was extensive cyclin-D1 and subset CD10 immunopositivity. FISH showed *YWHAE* amplification but without rearrangement. Interestingly, we found only two other reported cases of pleomorphic HGESS with *YWHAE* gene amplification upon review of 259 cases from cBioPortal database, one of which was reported as carcinosarcoma with heterologous elements. Of note, all three *YWHAE* amplified cases were diagnosed at high-stage and succumbed to disease within six months. Our case appears to be the third case of *YWHAE*-amplified pleomorphic HGESS, possibly a new variant of uterine sarcoma with aggressive biologic behavior that needs further evaluation.

**Keywords:** High-grade endometrial stromal sarcoma, pleomorphic, YWHAE amplification

## Introduction

Uterine sarcomas are rare tumors comprising 3-7% of uterine malignancies [1, 2], of which leiomyosarcoma is the most common [3]. Endometrial stromal sarcoma (ESS), malignant mesenchymal neoplasms of endometrial stromal derivation, comprises less than 10% of all uterine sarcomas [4, 5]. They are often diagnosed in patients presenting with abnormal uterine bleeding, pelvic pain, and/or a mass; occasionally, they may present in asymptomatic patients as well as in the form of metastatic lesions in the lung or ovary. Most patients with ESS have no known risk factors, however, prior pelvic irradiation, hereditary cancer syndromes, prolonged estrogen exposure, obesity, and diabetes can be associated with an increased risk of ESS.

Endometrial stromal tumors are of four subtypes per the WHO classification of 2020: endometrial stromal nodule (ESN), low-grade ESS (LGESS), high-grade ESS (HGESS), and undifferentiated uterine sarcoma (UUS). The ESN is benign, usually found in the peri-menopausal period, has a well-circumscribed border, and is histopathologically similar to proliferative-

phase endometrial stroma composed of uniform small cells with scant cytoplasm, round to ovoid nuclei, inconspicuous nucleoli, and diffuse peri-arteriolar whorling. Less than three finger-like projections or adjacent nests are compatible with ES nodules whereas lymphovascular invasion would exclude this diagnosis [3]. LGESS is similar to ESN in that it histologically resembles proliferating endometrial stromal cells with minimal cellular atypia and low mitotic activity (<5/10 HPF) but exhibits permeative infiltration of myometrium and/or lymphovascular invasion [1, 3]. These tumors tend to occur in slightly younger women between the ages 45 and 55 relative to HGESS [6]. Tumor cells are typically diffusely immunopositive for CD10, WT-1, often for smooth muscle actin, estrogen receptor (ER) and progesterone receptor (PR), and occasionally for desmin, but negative for h-caldesmon. Histologic variations include smooth muscle nodules with starburst pattern, fibromyxoid change, sex cord-like differentiation (granulosa and sertoli like cells), and proliferative endometrioid-like glands. The most common chromosomal aberration in ES and LGESS involves t(7;17)(q21;q15) which results in the fusion of *JAZF1* and *SUZ12*. Other genes that can be rearranged in LGESS but not in ES nodule include *PHF1::JAZF1*, *EPC1::PHF1*, *MEAF6::PHF1, JAZF1::BCORL1, BRD8::PHF1,* and *ZC3H7B::BCOR* [7]. Prognosis of LGESS depends mainly upon the tumor stage with 90% 5-year disease-specific survival for stages I and II, but only 50% for stages III and IV.

HGESS, which was previously categorized under undifferentiated stromal sarcoma in the 2003 WHO classification, was re-classified in 2014 and remains as such in the 2020 WHO classification with the identification of the fusion *YWHAE::NUTM2A/B* t(10;17)(q22;p13). HGESS is clinically aggressive, often associated with extrauterine disease, and reportedly has a median progression-free survival (PFS) of 7 to 11 months and overall survival (OS) of 11 to 23 months [8]. It is histologically characterized by confluent permeative and destructive deep myometrial invasion, frequent necrosis, lymphovascular invasion, significant nuclear atypia, and mitotic activity of >10 per 10 HPF. It consists mostly of high-grade rounded cells in sheets and irregular nests, with a minor low-grade fibromyxoid spindle cell component [3]. These sarcomas are commonly diffusely (>70% nuclei) Cyclin D1 and BCOR protein immunopositive, but negative for CD10, ER, and PR. C-kit expression without DOG1 is associated with a worse prognosis. The most common chromosomal abnormality associated with HGESS is a t(10;17), resulting in *YWHAE::NUTM2A/B* gene fusion. Less common is HGESS with internal tandem duplication (ITD) of *BCOR* gene that occurs in younger patients and shows uniform nuclear features [8]. *YWHAE::NUTM2A/B* fusion is mutually exclusive with *JAZF1/SUZ12/EPC1/PHF1* gene rearrangements, as well as *BCOR*-Internal Tandem Duplication (*BCOR*-ITD) [3]. The infrequent HGESS with *ZC3H7B::BCOR* gene fusions shows significant morphologic overlap with myxoid leiomyosarcomas [9]. HGESS with the *YWHAE* rearrangement and *BCOR*-ITD generally have a prognosis intermediate between LGESS and UUS, yet with frequent recurrence often within a year of diagnosis [3, 10]. In contrast to LGESS, cytoreduction has a positive impact on survival in HGESS.

WHO 2020 defines UUS as “a tumor arising in the endometrium or myometrium, lacking any resemblance to proliferative-phase endometrial stroma, with high-grade cytological features and with no specific type of differentiation” [3]. USS is common in post-menopausal women. Patients with USS often show large (>10 cm) polypoid uterine mass, destructive myometrial invasion, and high stage (stage III/IV) at presentation. Tumor cells are typically present in sheets with marked cytologic atypia, high mitotic activity, lymphovascular invasion, and extensive hemorrhage and necrosis. Tumor cells are variably CD10 immunopositive. Cyclin D1 staining can be diffuse but in those cases the tumor is also typically positive for CD10 (unlike HGESS). ER and PR are weakly positive or negative. Focal actin, desmin, keratin or EMA may be seen [3]. They typically have complex but non-specific chromosomal abnormalities [1]. UUS is considered a diagnosis of exclusion and has poor prognosis even at a lower stage [1, 3, 11].

In this study, we report a case of a pleomorphic high-grade ESS found to have a novel *YWHAE* gene amplification in the absence of *YWHAE* rearrangement.

## Case report

A 66-year-old female presented with a history of post-menopausal bleeding and an enlarging

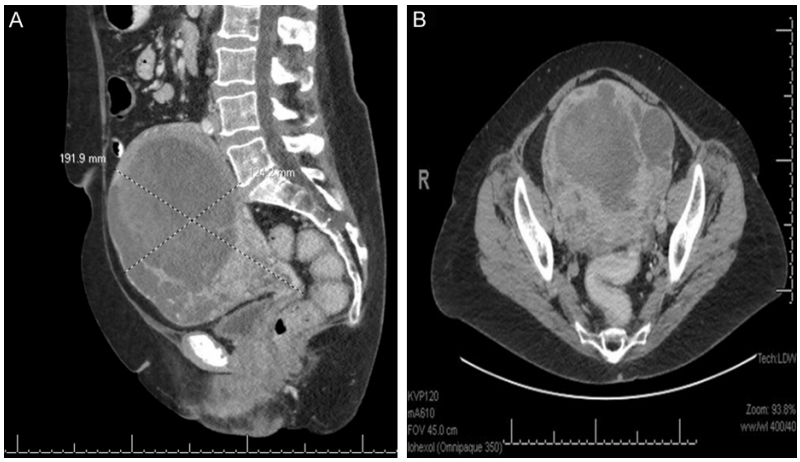


**Figure 1.** CT scan. A: Sagittal plane. Heterogeneous solid mass with myometrial invasion (arrow). B: Axial plane. Infiltrative myometrial lesion with solid and cystic areas (arrow).

abdominal mass. A CT scan revealed a heterogeneous solid and cystic mass lesion in her uterus, with evidence of diffuse myometrial involvement (**Figure 1**). An endometrial biopsy revealed a high-grade sarcomatous malignancy. A therapeutic total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node dissection (TAH/BSO/PLND/omentectomy) was performed. Pathologic examination showed a grossly variegated mass with yellow-white circumscribed central portion with areas of hemorrhage and necrosis, and peripheral ill-defined tan-red gelatinous, slightly friable necrotic portion. Histopathologic examination showed a variably hypercellular tumor with tongue-like destructive myometrial invasion. It was composed of variably formed haphazard fascicles with microcysts. Tumor cells exhibited moderate to marked pleomorphism, scattered multinucleated tumor giant cells, and high mitotic activity (>10/10 HPF) including many atypical mitotic figures (**Figure 2**). There was no evidence of extrauterine disease.

Immunohistochemistry showed tumor cells to be diffusely positive for Cyclin D1 with only patchy labeling for CD10 in a small subset of tumor cells (**Figure 3**). Tumor cells were negative for estrogen receptor, desmin, myogenin, and pankeratin (AE1/AE3). Fluorescence in-situ hybridization (FISH) did not find any rearrangement of the *YWHAE* or *PH1* gene regions, but instead showed amplification of the *YWHAE* gene in the tumor cells. The presence of a deeply myoinvasive, high-grade, pleomorphic, poorly differentiated sarcoma with the aforementioned morphology and immunophenotype in association with *YWHAE* amplification overall favored HGESS over the morphologic differential diagnoses of high-grade leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, or UUS. Thus, the patient was diagnosed with HGESS with *YWHAE* amplification.

The patient was treated with four cycles of chemotherapy paclitaxel/carboplatin. Follow-up CT scan 6-months post TAH/BSO/PLND/omentectomy revealed local recurrence of pelvic mass with ureteral obstruction and metastatic disease involving the bilateral lungs, mesentery, and inguinal and retroperitoneal areas. She was further treated with doxorubicin/cisplatin/ifosfamide before transitioning to hospice care.

## Discussion

Endometrial stromal sarcomas are rare intrauterine malignancies that make up less than 10% of all uterine sarcomas. HGESS is defined by the World Health Organization (WHO) as “a malignant tumor of endometrial stromal derivation with high-grade round cell morphology sometimes associated with a low-grade spindle cell component that is mostly fibromyxoid” [3]. Patients range in age from 28-67 (mean 50), often present with abnormal uterine bleeding, and can be associated with enlarged uterus or pelvic mass with pain. Grossly, HGESS are intracavitary polypoid and/or mural masses with a median size of 7.5 cm; fleshy cut surfaces may have hemorrhage and necrosis and they often show extra-uterine extension [3]. HGESS was re-classified in the 2014 WHO Classification with the identification of *YWHAE::NUTM2A/B* gene fusion, and accordingly is currently diagnosed on the basis of histopathologic, immunohistochemical, and molecular features. HGESS tends to have confluent, permeative, and destructive deep myometrial invasion often into the outer half with necrosis

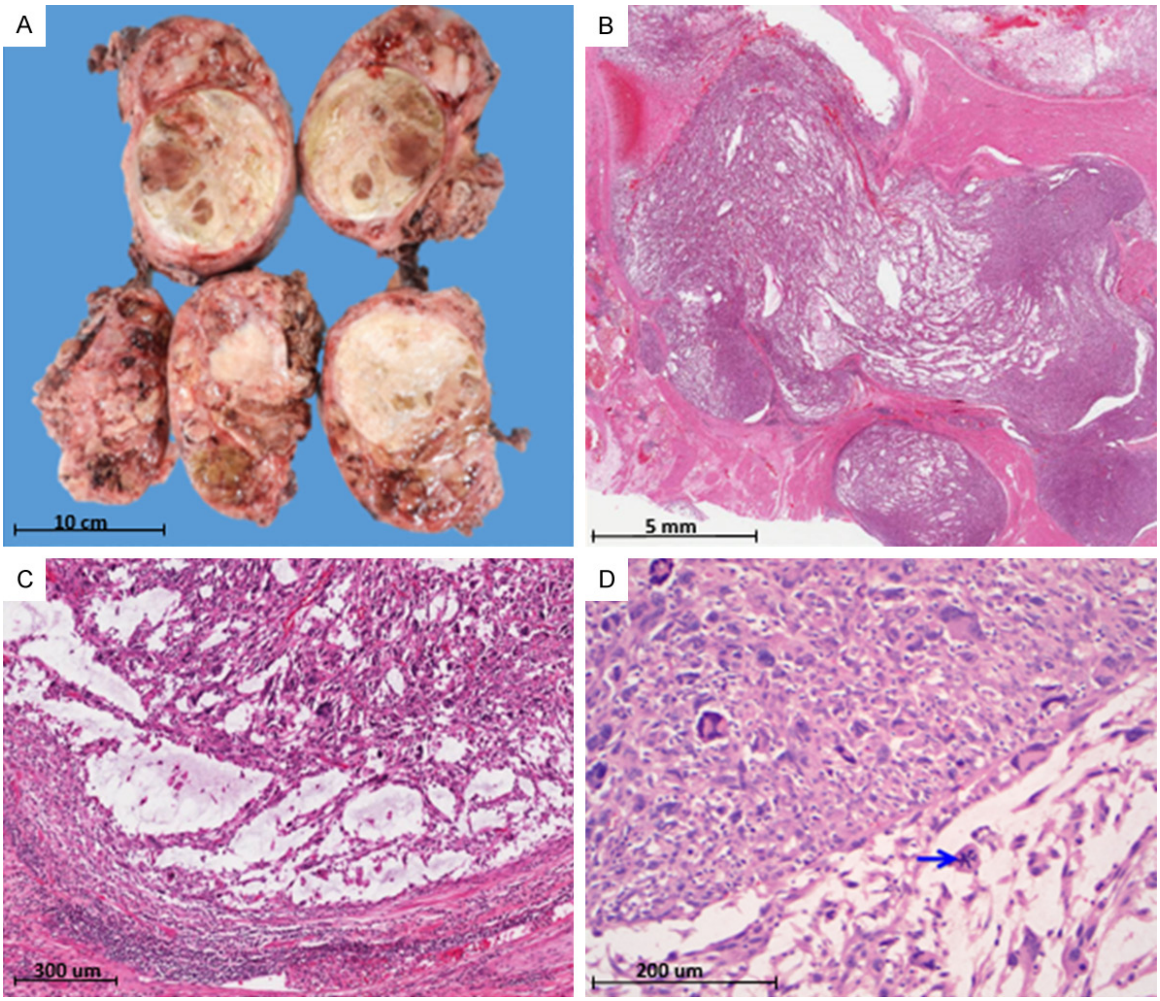


**Figure 2.** Gross and microscopic image. A. Gross appearance: Variegated cut surfaces of the solid-cystic tumor mass with yellow white circumscribed central portion, and peripheral ill-defined tan-red gelatinous friable portion, both with areas of necrosis and hemorrhage. B. Tumor with irregular tongue-like destructive myometrial invasion (×10). C. Haphazard ill-defined fascicles of hypercellular tumor with scattered microcysts (×100). D. Moderate to marked pleomorphism with scattered multinucleated tumor giant cells seen in both solid and microcystic portion of the tumor. Note atypical mitotic figure (arrow) (×200).

and lymphovascular invasion. Tumor cells are predominantly high-grade, rounded, arranged in hypercellular, variably formed nests and sheets with interspersed capillary networks with occasion pseudo-glandular, rhabdoid or primitive neuroectodermal differentiation. The rounded cells possess modest eosinophilic to granular cytoplasm, irregular nuclei with granular/vesicular chromatin, and variably distinct nucleoli [3]. The tumor cells show significant nuclear atypia and a mitotic activity of >10 per 10 HPF. Additionally, the rounded tumor cells may be variably intermixed with a minor low-grade fibromyxoid spindle cell component. The high-grade sarcoma component is often Cyclin D1 and c-kit positive by immunohistochemistry, and negative for CD10, ER, PR, and DOG1. In contrast, the low-grade spindle cell component is positive for CD10, ER, PR and more heterogeneously positive for Cyclin D1 [3, 9]. Histopathology on the current case showed a variably hypercellular tumor with tongue-like permeative and destructive invasion of >50% myometrial thickness with associated hemorrhage and necrosis. Tumor cells exhibited moderate to marked pleomorphism, scattered multinucleated tumor giant cells, and a high mitotic activity (>10 per 10 HPF) including atypical mitosis. No low-grade tumor component was identified. The tumor was diffusely Cyclin-D1

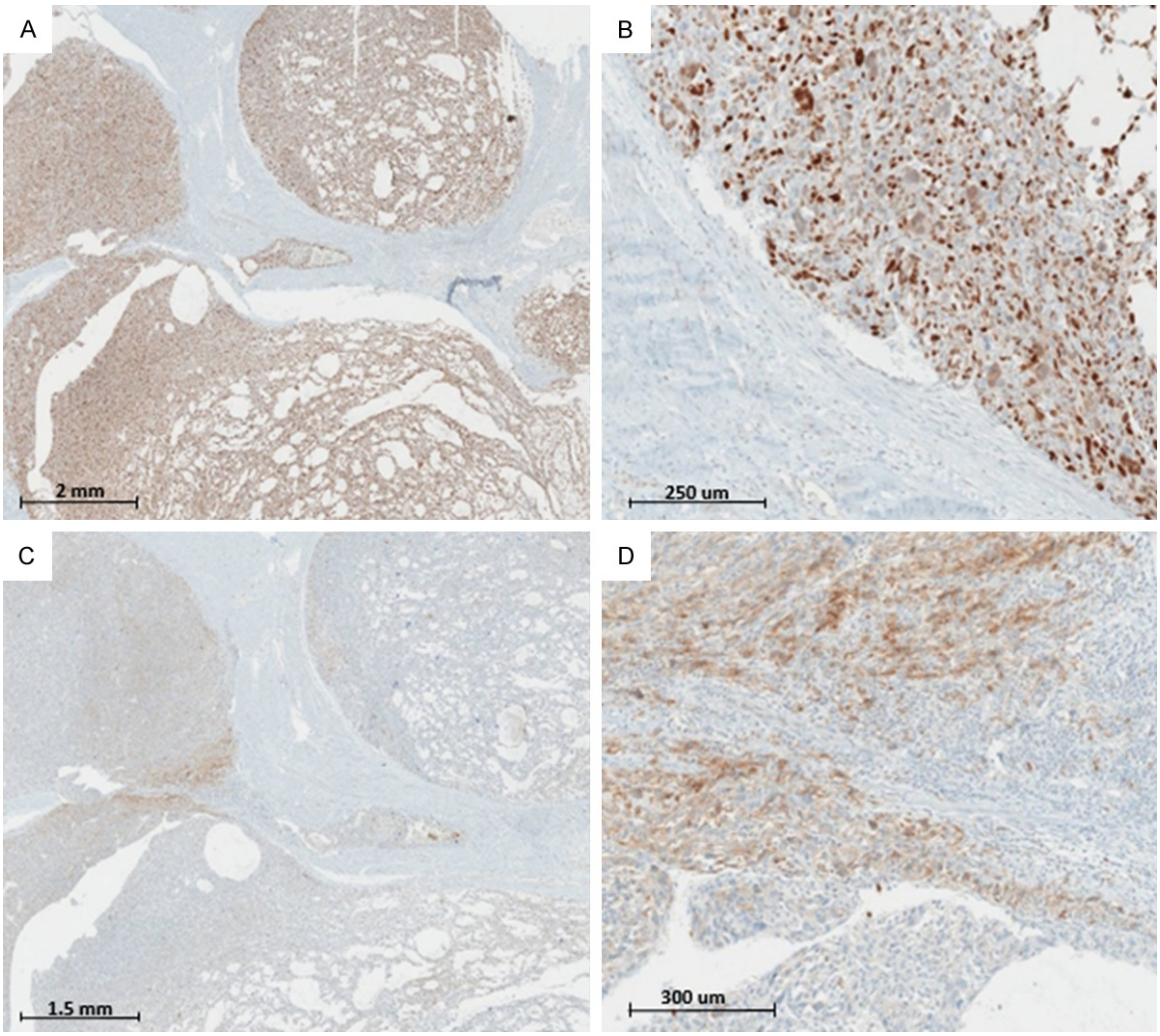


**Figure 3.** Immunohistochemical staining. A. Diffuse nuclear immunostaining for Cyclin D1 in tumor cells (×20). B. Nuclear immunostaining for Cyclin D1 in majority of tumor cells (×200). C. Patchy CD10 immunostaining in a small subset of tumor cells (×20). D. Patchy CD10 cytoplasmic immunostaining in a small subset of tumor cells (×200).

immunopositive with a subset of CD10 staining, but was negative for ER and PR. Thus, the tumor morphology and immunophenotype favored the diagnosis of HGESS over UUS.

Three morphologic subgroups have been described within HGESS [12]: group 1 includes tumors with a component that is similar to LGESS that transitions abruptly into a higher-grade component; group 2 describes tumors composed exclusively of high-grade rounded cells with uniform nuclear features but with a permeative pattern of infiltration; group 3 tumors are similar to the second group but with enlarged round to ovoid cells, smooth nuclear membranes and chromatin clearing without prominent nucleoli and are commonly associated with lymphovascular invasion and *YWHAE* rearrangement. The prognosis of all subtypes of HGESS is often poor despite therapy due to the aggressive nature of the tumors [5, 12]. This patient's HGESS is most consistent with the third subgroup as it demonstrated extensive tongue-like destructive invasion into the myometrium, necrosis and high-grade histology with moderate to marked pleomorphism, and high mitotic activity including atypical mitotic figures.

HGESS is typically associated with t(10;17), a translocation between a 14-3-3 protein (*YWHAE*), a group of regulatory proteins for signaling pathways, and *NUTM2A/B* (alias *FAM22A/B)* [13]. *YWHAE* is a highly regulated

gene and conducts a wide array of cellular functions related to growth, mitosis, and cell survival, with varied roles depending on the cytoplasmic (e.g., insulin dependent glucose uptake via the GLUT4 insulin shuttle) and nuclear localization (e.g., histone deacetylase binding). *NUTM2A/B* has a nuclear localization signal and is not carefully regulated, although its exact function is not defined. When fused, the tightly regulated oncogene *YWHAE* is translocated to the nucleus with the *NUTM2A/B* C-terminal nuclear localization signal, leading to aberrant signal transduction, cell division and growth, metabolism, and survival. Tumors with *YWHAE* rearrangements are associated with high-grade, high stage at presentation, and aggressive clinical behavior with disease recurrence [13]. However, our patient's HGESS lacked the classic *YWHAE* rearrangement and instead showed *YWHAE* amplification. The unique genomic anomaly in our case of an amplification of the *YWHAE* gene, which primarily encodes cytoplasmic protein regulators, may reflect its retained ability to promote tumorigenesis without the nuclear localization signal provided by *NUTM2A/B*.

According to the National Cancer Database, HGESS has a poor prognosis with median overall survival of 19.9 months and five-year overall survival of only 32.6% [14]. The molecular characteristics of HGESS are important for personalized chemotherapeutic protocol selection. There are limited data on treatment of these tumors; however, a case series reported that HGESS tumors with the *YWHAE* rearrangement have been shown to have a high degree of responsiveness to cytotoxic chemotherapeutic therapy [15]. Notably, HGESS with *YWHAE* rearrangement are particularly responsive to the anthracycline therapy and partially responsive to combination therapy with docetaxel and gemcitabine. Our patient was initially treated with an omentectomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. She was then started on carboplatin and paclitaxel combination therapy; however, after 4 cycles, CT scans showed continued progression of disease, so she was started on a round of doxorubicin, cisplatin, and ifosfamide. Despite multiple chemotherapy protocols, the progression continued, and the patient was discharged to hospice. The unique chromosomal abnormality of this tumor can be taken into account when evaluating the unresponsiveness of the patient's disease to chemotherapy. Further research to determine the function and significance of the *YWHAE* amplification in tumor progression may shed light on creating effective treatment protocols.

Interestingly, we found only two other reported cases of pleomorphic HGESS with *YWHAE* gene amplification from review of 259 cases from cBioPortal database, one of which was reported as carcinosarcoma with heterologous elements. Of note, all three *YWHAE* amplified cases were diagnosed at high-stage and succumbed to disease within six months. Moreover, our literature review identified one additional reported case of a pleomorphic ESS that was positive for *YWHAE* by RT-PCR but negative for a *YWHAE* gene rearrangement by FISH analysis, and an amplification of *YWHAE* would explain these seemingly discrepant results [16]. Of note, this patient also died within 6 months. This finding further indicates that pleomorphic histology, although rare, is acceptable within the spectrum of HGESS.

## Conclusion

*YWHAE::NUTM2 (alias YWHAE::FAM22)* has recently come to be recognized as characteristic of HGESS. The finding of *YWHAE* amplification without rearrangement in the current case expands the molecular spectrum of HGESS while presenting an alternative molecular pathway for its pathogenesis. Our case appears to be the third case of *YWHAE*-amplified pleomorphic HGESS, possibly a new variant of uterine sarcoma with aggressive biologic behavior that needs further evaluation.

## Acknowledgements

Written informed consent was obtained from the patient at the time of management at our institution.

## Disclosure of conflict of interest

None.

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## References


[1] Benson C and Miah AB. Uterine sarcoma-current perspectives. Int J Womens Health 2017; 9: 597-606.

[2] Nama N, Cason FD, Misra S, Hai S, Tucci V, Haq F, Love J, Ullah A, Peterson P, Grishko FF, Akbar W, Khaliq K and Waheed A. Carcinosarcoma of the Uterus: a study from the surveillance epidemiology and end result (SEER) database. Cureus 2020; 12: e10283.

[3] Kurman RJ, Carcangiu ML, Herrington CS and Young RH. WHO classification of tumours of female reproductive organs, 5th edition. Chapter 5: tumours of the uterine corpus: mesenchymal tumors. Lyon, France: International Agency for Research on Cancer; 2014. pp. 135-147.

[4] Chan JK, Kawar NM, Shin JY, Osann, K, Chen LM, Powell CB and Kapp DS. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer 2008; 99: 1210-5.

[5] Eamudomkarn N, Itarat Y, Kleebkaow P and Kietpeerakool C. A case report of high-grade endometrial stromal sarcoma: a rare cause of abnormal uterine bleeding in a young woman. Case Rep Obstet Gynecol 2018; 2018: 5906760.

[6] Jain R, Batra S, Ahmad A, Elahi AA, Gupta M and Saith P. Low grade endometrial stromal sarcoma: a case report. Iran J Med Sci 2015; 40: 81-4.

[7] Capozzi VA, Monfardini L, Ceni V, Cianciolo A, Butera D, Gaiano M and Berretta R. Endometrial stromal sarcoma: a review of rare mesenchymal uterine neoplasm. J Obstet Gynaecol Res 2020; 46: 2221-36.

[8] Pautier P, Nam EJ, Provencher DM, Hamilton AL, Mangili G, Siddiqui NA, Westermann AM, Reed NS, Harter P and Ray-Coquard I. Gynecologic Cancer InterGroup (GCIG) consensus review for high-grade undifferentiated sarcomas of the uterus. Int J Gynecol Cancer 2014; 24 Suppl 3: S73-7.

[9] Hoang LN, Aneja A, Conlon N, Delair DF, Middha S, Benayed R, Hensley ML, Park KJ, Hollmann TJ, Hameed MR, Antonescu CR, Soslow RA and Chiang S. Novel high-grade endometrial stromal sarcoma: a morphologic mimicker of myxoid leiomyosarcoma. Am J Surg Pathol 2017; 41: 12-24.

[10] Mariño-Enriquez A, Lauria A, Przybyl J, Ng TL, Kowalewska M, Debiec-Rychter M, Ganesan R, Sumathi V, George S, McCluggage WG, Nucci MR, Lee CH and Fletcher JA. BCOR internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol 2018; 42: 335-341.

[11] Hrzenjak A, Dieber-Rotheneder M, Moinfar F, Petru E and Zatloukal K. Molecular mechanisms of endometrial stromal sarcoma and undifferentiated endometrial sarcoma as premises for new therapeutic strategies. Cancer Lett 2014; 354: 21-7.

[12] Sciallis AP, Bedroske PP, Schoolmeester JK, Sukov WR, Keeney GL, Hodge JC and Bell DA. High-grade endometrial stromal sarcomas: a clinicopathologic study of a group of tumors with heterogenous morphologic and genetic features. Am J Surg Pathol 2014; 38: 1161-72.

[13] Lee CH, Ou WB, Mariño-Enriquez A, Zhu M, Mayeda M, Wang Y, Guo X, Brunner AL, Amant F, French CA, West RB, McAlpine JN, Gilks CB, Yaffe MB, Prentice LM, McPherson A, Jones SJ, Marra MA, Shah SP, van de Rijn M, Huntsman DG, Dal Cin P, Debiec-Rychter M, Nucci MR and Fletcher JA. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. Proc Natl Acad Sci U S A 2012; 109: 929-34.

[14] Seagle BL, Shilpi A, Buchanan S, Goodman C and Shahabi S. Low-grade and high-grade endometrial stromal sarcoma: a national cancer database study. Gynecol Oncol 2017; 146: 254-262.

[15] Hemming ML, Wagner AJ, Nucci MR, Chiang S, Wang L, Hensley ML and George S. YWHAE-rearranged high-grade endometrial stromal sarcoma: two-center case series and response to chemotherapy. Gynecol Oncol 2017; 145: 531-535.

[16] Croce S, Hostein I, Ribeiro A, Garbay D, Velasco V, Stoeckle E, Guyon F, Floquet A, Neuville A, Coindre JM, MacGrogan G and Chibon F. YWHAE rearrangement identified by FISH and RT-PCR in endometrial stromal sarcomas: genetic and pathological correlations. Mod Pathol 2013; 26: 1390-400.