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A rare case of high-grade endometrial stromal sarcoma initially misdiagnosed as a uterine fibroid in a postmenopausal woman

Arianna R Gregg

ABSTRACT

Introduction: High-grade endometrial stromal sarcoma (HG-ESS) is a rare and aggressive malignant neoplasm that has a poor prognosis and accounts for 0.2% of uterine malignancies. There is a lack of available information on HG-ESS due to its high case fatality rate. Due to the poor prognosis associated with HG-ESS, it is important to diagnose HG-ESS in its early stages.

Case Report: In this case report, we describe the case of a 63-year-old postmenopausal woman who presented with a pelvic mass and postmenopausal bleeding. The patient's past history included a fibroid for which the patient underwent a successful uterine fibroid embolization. The patient underwent a pelvic ultrasound and an endometrial biopsy prior to gynecological consult. Both were inconclusive and led to an initial diagnosis of a uterine fibroid. After a gynecological consult and an additional biopsy, pathological examination revealed high-grade neoplastic cells that expressed strong and diffuse nuclear BCL1/Cyclin D1. The pattern of diffuse cyclin D1 expression and negative CD10 was suggestive of the *YWHAE*-rearranged subtype of HG-ESS. The combined morphologic and immunophenotypic features were consistent with a high-grade endometrial stromal sarcoma with fluorescence in situ hybridization (FISH) positivity for *YWHAE* gene rearrangement and FISH negativity for BCOR gene rearrangement. The patient underwent a robotic-assisted modified radical hysterectomy, radical pelvic tumor resection, bilateral salpingo-oophorectomy, sentinel pelvic lymph node dissections, and an appendectomy. The resulting surgical pathologic diagnosis was HG-ESS stage 1. Currently, no adjuvant therapy is recommended given negative margins with stage 1 status.

Conclusion: High-grade endometrial stromal sarcoma is a rare clinical entity in postmenopausal women which is initially misdiagnosed but should be included in the differential diagnosis of necrotic masses.

Keywords: Fibroid, HG-ESS, Postmenopausal

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Arianna R Gregg[1], BS

Affiliation: [1]Department of OB/GYN, Sutter Medical Center, Sacramento, CA, USA.

Corresponding Author: Arianna R Gregg, BS, 6900 Sharlands Avenue, Reno, NV 89523, USA; Email: annargregg@me.com

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INTRODUCTION

A high-grade endometrial stromal sarcoma (HG-ESS) is a rare and uncommon type of uterine sarcoma [1]. This malignant sarcoma originates from the stromal cells in the endometrium and commonly presents in the uterine cavity [1]. Endometrial stromal sarcomas make up 0.2% of uterine malignancies [2]. While there are a prolific number of cases involving low-grade endometrial stromal sarcomas, there is insignificant data on high-grade endometrial stromal sarcomas most likely due to the rapid development, the prevalent metastasis, the presentation in advanced stages and the high fatality rate [3].

Endometrial stromal sarcomas are most often observed in younger, premenopausal women between

the ages of 45 and 50 and present with vaginal discharge and bleeding [4]. Abnormal genital bleeding is often attributed to the uterus and is no longer considered normal after menopause. The most common cause of postmenopausal bleeding is atrophy of the endometrium or the vaginal mucosa [5]. Other common etiologies include endometrial hyperplasia, endometrial polyps, and submucosal leiomyomas [5]. When only using ultrasonography and magnetic resonance imaging (MRI), it is difficult to confirm a differential diagnosis between uterine sarcoma and benign leiomyoma [3].

Although rare, HG-ESS should be considered in the differential diagnosis when abnormal uterine bleeding in postmenopausal women and masses with a heterogeneous appearance present. Here, we describe a case of HG-ESS in a postmenopausal woman who presented with a pelvic mass and postmenopausal bleeding.

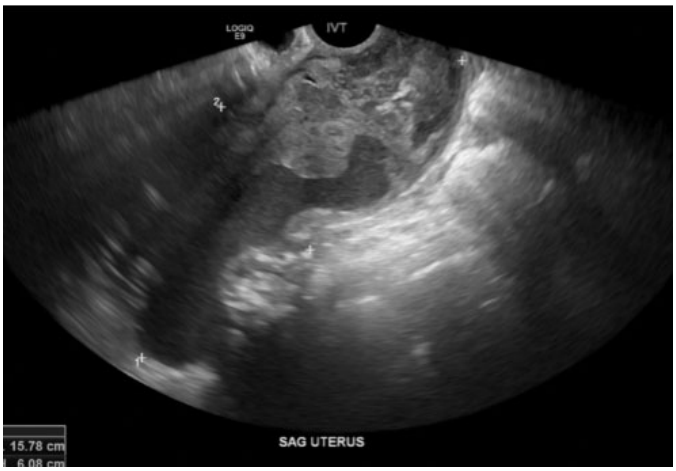

Figure 1: Sagittal-uterus ultrasound shows a 15.8×6.1×8.1 cm amorphous ill-defined soft tissue mass on the midline pelvis with solid and cystic components and with a possible enlarged uterus.

CASE REPORT

A 63-year-old, G1P0, woman presented to our outpatient OB/GYN office with postmenopausal bleeding per vagina and a pelvic mass. The patient's past history included a large fibroid for which the patient underwent a uterine fibroid embolization in 2005. A month prior to the patient's presentation at our clinic, they presented at their primary care physician with irregular spotting and suprapubic fullness and pressure. Subsequently, the patient had a pelvic ultrasound which revealed a 15.8×6.1×8.1 cm ill-defined soft tissue mass on the midline pelvis with solid and cystic components and with a possible enlarged uterus (see Figure 1). An endometrial biopsy was recommended. Prior to the endometrial biopsy, the patient's preoperative diagnosis included a uterine fibroid. The subsequent endometrial biopsy with the primary care physician revealed significantly degenerated and partially necrotic short-spindled cells with fibrinoid debris. Due to the significant cellular degeneration and partial necrosis, the cellular details of the short-spindled cells were difficult to evaluate and therefore resulted in inconclusive pathology. Significant bleeding from the cervical os was suspected to be due to the known fibroids and likely was benign. An additional biopsy and MRI were recommended and the patient was referred to our outpatient OB/GYN office for further care.

Upon presentation at our outpatient OB/GYN office, the patient reported that the vaginal bleeding increased in the past two weeks and that they had passed a few small pieces of tissue with increased brown and mucus-like discharge. The patient's gynecological examination revealed an enlarged uterus. On bimanual exam, a soft tissue mass was palpated and found to be protruding through the cervix. Upon palpation of the mass, profuse bleeding was observed. The cervix was not visualized, only the necrotic and friable mass was visible. Portions of the mass that separated were sent for further pathologic review. Based on the previous pathology with spindled cells, a possible uterine sarcoma was suspected, and the patient was referred to a gynecologic oncologist.

The pathological examination revealed that the high-grade neoplastic cells expressed strong and diffuse nuclear BCL1/Cyclin D1. Studies showed negative staining for PAX8, desmin, myogenin, PAX7, PMS2, MSH6, BRG, INI, and CD45. The low-grade proliferation lacked increased BCL1 expression. The pattern of diffuse cyclin D1 expression and negative CD10 in the high-grade neoplastic cells was suggestive of the *YWHAE*-rearranged subtype of HG-ESS. The combined morphologic and immunophenotypic features were consistent with a high-grade endometrial stromal sarcoma with FISH positivity for *YWHAE* gene rearrangement and FISH negativity for *BCOR* gene rearrangement.

Further hematoxylin-eosin stained (H&E) sections of the necrotic endometrial mass biopsy showed a hypercellular proliferation of plump spindled to epithelioid cells arranged in a vaguely nested to diffuse sheet-like architecture with a delicate vasculature network. The malignant cells were characterized cytologically by relatively uniform ovoid nuclei, fine nuclear chromatin, and scant lightly eosinophilic to clear cytoplasm. Frequent mitotic figures were seen. There was a background of hemorrhage, acute inflammation, and tumor necrosis. A less cellular endometrial stromal proliferation comprised of only mildly atypical spindle cells with round to oval nuclei, more abundant cytoplasm, and low mitotic activity in an adjacent area was suggestive of a more conventional low-grade stromal component.

Immunohistochemical studies demonstrated that the malignant cells expressed CD56 and patchy (non-diffuse) p16. The studies were negative for pancytokeratin, cytokeratin (AE1/AE3), Napain A, calponin, muscle-specific actin, calretinin, inhibin, chromogranin, synaptophysin, EMA, S-100 protein, and HMB-45. CD10, estrogen receptor (ER), and progesterone receptor

(PR) highlighted the adjacent low-grade endometrial stromal proliferation and were negative in the high-grade malignant cells. The immunohistochemical stain for p53 showed a wild-type expression pattern. The pathology examination resulted in the preoperative diagnosis of a high-grade endometrial stromal sarcoma with confirmed FISH positive *YWHAE* gene rearrangement and FISH negative for *BCOR* gene rearrangement.

At hysterectomy, dense pelvic adhesions, retroperitoneal fibrosis and extensive right ureterolysis were noted. The surgical procedure included robotic-assisted radical hysterectomy, radical pelvic tumor resection, bilateral salpingo-oophorectomy, appendectomy, and sentinel pelvic lymph node dissections. The presacral and left pelvic sentinel lymph nodes were negative for metastatic tumor. On the sigmoid colon, benign fibroadipose tissue with dense chronic and histiocytic inflammation was excised and no malignancy was identified. Benign fibroadipose tissue with reactive change was identified on the right pelvic lymph node but was negative for metastatic tumor. A left perirectal benign adhesion was excised with dense chronic and histiocytic inflammation and hemorrhage. All parametria and vaginal resection margins were negative. No extrauterine involvement or lymphovascular invasion was identified. Right fallopian tube and ovary showed extensive acute and chronic inflammation with abscess formation and dense xanthogranulomatous inflammation. Focal areas of ovarian type stroma were present. The findings suggested near complete replacement of ovarian tissue by abscess and inflammation. Additional Immunohistochemistry (IHC) staining for cyclin-D1 (bcl-1), CD10, and CD117 were performed with reactive controls on block A3 along with staining for AE1/AE3, cyclin-D1 and CD68 which were performed with reactive controls on blocks D1, F2, G3, and G14. The surgical pathology report confirmed the diagnosis of a high-grade endometrial stromal sarcoma, 11.5 cm in aggregate.

The postoperative clinical course was uneventful. The patient was told to follow up with the gynecologic oncologist in three months for ongoing surveillance of the endometrial sarcoma. Additional imaging was recommended as part of the surveillance moving forward. No adjuvant therapy was recommended given the negative margins with stage 1 status.

DISCUSSION

Uterine fibroids are characterized as noncancerous growths of the uterus and commonly present with genital bleeding but genital bleeding is no longer considered normal after menopause [5]. Between 1% and 14% of postmenopausal bleeding will be secondary to endometrial cancer [6]. In more than 90% of postmenopausal women with endometrial cancer, vaginal bleeding is the presenting sign [6]. When only using ultrasonography and MRI, it is difficult to confirm a differential diagnosis between uterine sarcoma and benign leiomyoma [3]. Due to the lack of characteristic imaging and clinical manifestations, HG-ESS is often misdiagnosed prior to operation [7]. In a series from 1990 to 2002, 6 out of 15 women with a median age of 34 had an original missed diagnosis that was determined to be an endometrial stromal sarcoma only after consultation with a pathologist with a special interest in gynecologic pathology [8]. Cellular leiomyoma, cellular intravenous leiomyomatosis, adenomyosis with sparse glands, metastatic carcinoma, and lymphomas are lesions considered in the differential diagnosis of endometrial stromal sarcomas [8]. In this case report, we describe a case of HG-ESS in a 63-year-old woman who was initially diagnosed with uterine fibroids and presented with postmenopausal bleeding and a pelvic mass.

An endometrial stromal sarcoma is a rare malignant neoplasm that represents less than 0.2% of uterine malignancies [2]. The incidence of HG-ESS is extremely rare. As of 2017, there had been less than 100 reported cases of ovarian endometrial stromal sarcomas with almost all of them presenting as low grade [9]. Due to the extremely low incidence of HG-ESS, specific clinical manifestations and biomarkers are lacking. Some of the atypical manifestations that have been reported include abnormal genital bleeding, abdominal pain, and pelvic mass with some cases presenting as asymptomatic [7]. Most patients present with advanced stages at initial diagnosis [7]. The average age of patients with HG-ESS diagnosis is about 50 years old [7]. The unique finding in our report is a stage 1 HG-ESS presenting in a 63-year-old postmenopausal woman who was initially misdiagnosed.

An endometrial stromal sarcoma is a genetically heterogeneous group of uterine sarcomas [10]. In 2014, The World Health Organization classified endometrial stromal sarcomas into three classes based on pathological and clinical features: low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS) [11]. High-grade endometrial stromal sarcomas harbor t(10;17)(q22;p13) resulting in *YWHAE*-NUTM2A/B genetic fusion which makes HG-ESS molecularly and prognostically distinct compared to other ESS [2]. The *YWHAE* gene arrangement in HG-ESS is characterized by a monomorphic proliferation of round cells in a nested pattern. These round cells are larger than those of LG-ESS and contain a slight irregular nuclear contour, fine evenly dispersed chromatin with nuclear clearing, lack of prominent nucleoli, and scant to moderate cytoplasm [2]. Cyclin D1 is a sensitive and specific diagnostic marker of the *YWHAE*-rearranged subtype that can be used to evaluate high-grade uterine sarcomas [2]. *BCOR* internal tandem duplication (ITD) is an oncogenic alternative to the *YWHAE*-NUTM2A/B genetic fusion and composes a unique subtype of HG-ESS [12]. The *BCOR* ITD subtype is morphologically comprised of nonpleomorphic spindle cells blended with epithelioid and round cells and displays brisk mitotic activity and

necrosis [12]. A majority of LG-ESS harbor chromosomal rearrangements such as ZC3H7B-BCOR fusions which are absent in HG-ESS [2]. Less cellular endometrial stromal proliferation comprised of only mildly atypical spindle cells with round to oval nuclei, more abundant cytoplasm and low mitotic activity is suggestive of LG-ESS [2]. Positive CD10 when strong and diffuse and the presence of estrogen and progesterone receptors can also help to differentiate endometrial stromal nodules and LG-ESS from HG-ESS [13]. To differentiate between a uterine sarcoma and a benign leiomyoma, additional preoperative diagnostic procedures are required. Performing an ultrasound-guided needle biopsy can lead to a more accurate diagnosis when uterine tumors have suspected malignancy and appear heterogenous [3]. In most cases, a diagnosis is made postoperatively after a histopathological review to confirm the presence of t(10;17)(q22;p13) [14].

The pathological features of HG-ESS include a tumor marked with frequent mitotic activity (>20–30 mitoses/10 HP fields), loss of hormone receptors such as estrogen and progesterone, negative for smooth muscle markers, negative for CD10, positive for CD56 and diffusely positive for cyclin D1 [15]. In our patient, there was frequent mitotic activity, loss of estrogen and progesterone hormone receptors, a pattern of diffuse cyclin D1 expression with positive CD56 and negative CD10 which was partially suggestive of the *YWHAE*-rearranged subtype of HG-ESS and negative for the *BCOR* ITD subtype.

To the naked eye, HG-ESS has a fish-like surface along with areas of extensive bleeding and necrosis [2]. Microscopically, HG-ESS presents as a densely cellular tumor with nests and sheets containing a variable combination of high-grade round cell elements and lower-grade spindle cell elements [2]. The round cells display abnormal hyperchromatic or granular nuclei and minimal cytoplasm with only slight characteristics of endometrial stromal cell differentiation [2]. When trying to make a diagnosis based on immunophenotype, diffuse positive staining of cyclin D1 and CD56 along with negative CD10 and hormone receptors can be helpful to confirm the diagnosis of HG-ESS.

Due to the limited number of cases, the gold standard of treatment for HG-ESS has not been determined [16]. Current treatment involves surgery and adjuvant therapies such as chemotherapy and radiation therapy [16]. Retrospective reviews of patients with HG-ESS describe total abdominal hysterectomy with bilateral salpingo-oophorectomy as a promising treatment modality. Lymphadenectomy and adjuvant radiotherapy are often coupled with this treatment depending on the tumor stage [4]. According to the National Cancer Database, the survival rate of patients with HG-ESS remains poor [17]. The median overall survival was 19.9 months (95% CI, 17.1–22.1 months) with the overall five-year survival at only 32.6% (95% CI: 30.1–35.3%) [17]. Information regarding prognostic factors is limited but one study did find that a patient's age, tumor size, omission of lymphadenectomy, pathologically positive resection margins, and distant or nodal metastasis were negatively associated with survival. An additional study suggested that the stage of disease, minimum and average values of CA125, menopause, history of uterine leiomyoma, and endometriosis were independent risk factors impacting overall survival [14].

Current literature reports that most diagnoses of an endometrial stromal sarcoma occur in premenopausal women with a median age of 51 years [4]. Therefore, it is rare for HG-ESS to be diagnosed in a 63-year-old postmenopausal woman. Yet, it is common for HG-ESS to be misdiagnosed as a leiomyoma before operation. Sagae et al. [18] reported that 75% of the 22 endometrial stromal sarcomas were diagnosed pre-operatively as a leiomyoma. Obvious symptoms such as atypical vaginal bleeding, metrorrhagia, and uterine enlargement were found in most early-stage patients, but these clinical signs are not specific [18]. Cytological examinations were also insufficient in offering an early diagnosis. Pathological examination and biopsy can be useful for early detection. When patients with stage 1 endometrial stromal sarcoma had no residual disease postoperatively, the 5-year survival rates were high at 94.7% [18]. In early stage, total resection and no residual disease at surgery was the most important prognostic factor while postoperative adjuvant therapy had little effect on survival but information regarding treatment and prognostic factors remains scare due to the limited experience with endometrial stromal sarcomas [17]. Still, the prognosis of HG-ESS among postmenopausal women who were misdiagnosed with uterine leiomyoma is generally poor due to the disease presenting at a later stage. Patients among this subset succumb to the extensive metastases of the disease in a relatively short time period after surgery [14]. In our postmenopausal patient, there was no residual disease post-surgery and therefore no adjuvant therapy was needed given that the tumor was in an early stage.

CONCLUSION

A high-grade endometrial stromal sarcoma is a very rare pathological malignancy that is infrequently diagnosed preoperatively. It is most often misdiagnosed due to its lack of characteristic imaging and clinical manifestations. Its poor prognosis and extremely aggressive nature make early diagnosis in the initial stages essential to increase overall survival. This case report highlights HG-ESS as a rare yet possible cause of abnormal genital bleeding in postmenopausal women and thus should be considered in the differential diagnosis of necrotic cystic masses.

REFERENCES

1. Wang F, Lei R, Yang H, Guo M, Tan G. Endometrial stromal sarcoma: A clinicopathological analysis of 14 cases. Int J Clin Exp Pathol 2018;11(5):2799–804.
2. Ali RH, Rouzbahman M. Endometrial stromal tumours revisited: An update based on the 2014 WHO classification. J Clin Pathol 2015;68(5):325–32.
3. Shekhar S, Sharma C, Elhence P, Bansal S, Garg N. A case of high-grade endometrial stromal sarcoma: A poignant allegory. J Midlife Health 2019;10(4):209–12.
4. Li N, Wu LY, Zhang HT, An JS, Li XG, Ma SK. Treatment options in stage I endometrial stromal sarcoma: A retrospective analysis of 53 cases. Gynecol Oncol 2008;108(2):306–11.
5. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: A prospective cohort study. J Minim Invasive Gynecol 2014;21(5):799–803.
6. ACOG Committee Opinion No. 734: The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women with Postmenopausal Bleeding. Obstet Gynecol 2018;131(5):e124–9.
7. Zhang Y, Chen C, Ren M, Cong X, Li Z, Yang L. Treatment of uterine high-grade endometrial stromal sarcoma with apatinib combined with chemotherapy: A case report. Medicine (Baltimore) 2019;98(13):e15050.
8. Soto-Wright V, McLellan R. Chapter 46 - Uterine sarcomas. In: Bieber EJ, Sanfilippo JS, Horowitz Horowitz IR, editors. Clinical Gynecology. Philadelphia: Churchill Livingstone; 2006. p. 677–85.
9. Xie W, Bi X, Cao D, Yang J, Shen K, You Y. Primary endometrioid stromal sarcomas of the ovary: A clinicopathological study of 14 cases with a review of the literature. Oncotarget 2017;8(38):63345–52.
10. Lee CH, Mariño-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: A histologically high-grade and clinically aggressive tumor. Am J Surg Pathol 2012;36(5):641–53.
11. Kurman RJ, Carcangiu ML, Herrington CS. World Health Organisation Classification of tumours of the female reproductive organs. Jpn J Microbiol 2014;17:223–7.
12. Mariño-Enriquez A, Lauria A, Przybyl J, et al. BCOR internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol 2018;42(3):335–41.
13. McCluggage WG, Sumathi VP, Maxwell P. CD10 is a sensitive and diagnostically useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. Histopathology 2001;39(3):273–8.
14. Zhang YY, Li Y, Qin M, Cai Y, Jin Y, Pan LY. High-grade endometrial stromal sarcoma: A retrospective study of factors influencing prognosis. Cancer Manag Res 2019;11:831–7.
15. Horng HC, Wen KC, Wang PH, et al. Uterine sarcoma Part II-Uterine endometrial stromal sarcoma: The TAG systematic review. Taiwan J Obstet Gynecol 2016;55(4):472–9.
16. Leath CA 3rd, Huh WK, Hyde J Jr, et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. Gynecol Oncol 2007;105(3):630–4.
17. Seagle B-LL, Shilpi A, Buchanan S, Goodman C, Shahabi S. Low-grade and high-grade endometrial stromal sarcoma: A National Cancer Database study. Gynecol Oncol 2017;146(2):254–62.
18. Sagae S, Yamashita K, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology 2004;67(1):33–9.

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Arianna R Gregg – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be 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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Author declares no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.