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YWHAE-rearranged high-grade endometrial stromal sarcoma: Two-center case series and response to chemotherapy

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HIGHLIGHTS

- *YWHAE*-rearranged high-grade endometrial stromal sarcoma is an uncommon uterine malignancy.
- Identification of *t*(10;17)(q22;p13) together with histopathology can support this diagnosis.
- Metastatic *YWHAE*-rearranged HG-ESS appears quite sensitive to anthracycline-based chemotherapy.

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ABSTRACT

Objectives. *YWHAE*-rearranged high-grade endometrial stromal sarcoma (HG-ESS) is a rare, recently defined uterine sarcoma harboring *t*(10;17)(q22;p13) resulting in *YWHAE-NUTM2A/B* fusion. Chemotherapy sensitivity of metastatic *YWHAE*-rearranged HG-ESS is unknown. We reviewed the response to chemotherapy in women with *YWHAE*-rearranged HG-ESS to provide guidance for clinical management.

Methods. We retrospectively identified patients diagnosed with *YWHAE*-rearranged HG-ESS who received treatment for metastatic disease at our institutions. Cytogenetics or fluorescence in situ hybridization were performed in all cases to confirm rearrangement and, in conjunction with histopathology, a diagnosis of *YWHAE*-rearranged HG-ESS. Patient demographics, tumor histology, surgical procedures, radiation therapy, chemotherapy and treatment responses were collected.

Results. Seven patients were identified with *YWHAE*-rearranged HG-ESS and met criteria for inclusion in this study. The median age at diagnosis was 45 (range 42–47). All patients had undergone hysterectomy with bilateral salpingo-oophorectomy. FIGO stage at diagnosis was IVB in four patients and a single patient each at stage IIIB, II or I. Median follow-up for the cohort was 27 months (range 6–123). Six patients received anthracycline-based chemotherapy, with two of six achieving a complete radiologic response. One patient received gemcitabine and docetaxel, resulting in a partial response. For three patients who died from metastatic disease, survival from initial diagnosis was 33, 100 and 123 months.

Conclusions. For metastatic *YWHAE*-rearranged HG-ESS, prolonged disease control following diagnosis was seen, with notable responses to anthracycline-based therapy. This emphasizes the need for appropriate molecular testing of uterine mesenchymal malignancies and suggests that chemotherapy is an effective treatment option for metastatic *YWHAE*-rearranged HG-ESS.

1. Introduction

Endometrial stromal sarcomas (ESSs) are the second most common mesenchymal neoplasm of the uterus and constitute less than 2% of all uterine tumors [1,2]. ESSs are subdivided into low-grade and high-grade forms, which are distinguished by clinical behavior, histologic appearance, immunohistochemical features and chromosomal translocations. Low-grade ESS (LG-ESS) is characterized by an indolent course, with relapse common and typically treated with multimodal therapy. These tumors commonly express estrogen (ER) and progesterone (PR) receptors, and hormonal therapy is effective in their treatment [3].

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Several chromosomal translocations resulting in gene fusion have been identified in LG-ESS, with the most common being *JAZF1-SUZ12;* others include *JAZF1-PHF1*, *EPC1-PHF1* and *MEAF6-PHF1* [1]. These fusion genes all involve members of the Polycomb Group Family, either together or in combination with transcription factors.

High-grade ESS (HG-ESS), harboring *t*(10;17)(q22;p13) resulting in *YWHAE-NUTM2A/B* fusion [4], is a recently described and more aggressive neoplasm with a poorer prognosis compared to its low-grade counterpart. Patients with this tumor type typically present with vaginal bleeding, a mean age near 50 and advanced disease [5]. *YWHAE*-rearranged HG-ESS characteristically contains a morphologically high-grade but uniform round to epithelioid cell component and may show an associated low-grade fibroblastic/myxoid cell component. The morphologically high grade round to epithelioid cell component often shows brisk mitotic activity and necrosis, and typically expresses strong and diffuse cyclin D1 and KIT [6,7]. The *YWHAE* gene encodes the 14-3-3ε protein, which functions as a molecular scaffold to coordinate cellular signaling by binding to phosphoserine- or phosphothreonine-containing proteins. The *NUTM2A* and *NUTM2B* genes are located on chromosome 10q and bear 99% amino acid identity. The NUT (nuclear protein in testis) family consists of nuclear proteins with poorly described function. The fusion between *BRD4* or *BRD3* genes to *NUTM1* on chromosome 15 has been well described as the causative lesion in NUT midline carcinoma [8]. The fusion protein in *YWHAE*-rearranged HG-ESS has been shown to retain the functional domains of 14-3-3ε and, with fusion to the NUT proteins, prompt aberrant nuclear localization of 14-3-3ε [4]. How the fusion protein leads to a neoplastic cellular program has not yet been determined.

YWHAE-rearranged HG-ESS was added to the World Health Organization classification system in 2014 [1]. Because of this recent definition and the rare nature of this tumor, the clinical management of *YWHAE*-rearranged HG-ESS has not yet been described. Prior pathologic case series of translocation-confirmed HG-ESS [5,9,10] have not included modalities of treatment or responses to therapy. Many other reports describing case series of ESS have no or few translocation-confirmed cases [11–15]. Unlike LG-ESS which consistently express ER and PR and have demonstrated responses to hormonal therapy [3], *YWHAE*-rearranged HG-ESS stains variably for hormone receptors [5], with staining characteristically present in the morphologically low grade component. One case report of a HG-ESS with response to imatinib has been published [16], though the tumor was not tested for the *YWHAE-NUTM2A/B* rearrangement and may represent an alternative malignancy. Furthermore, no *KIT* or *PDGFRA* mutations have been found in *YWHAE-NUTM2A/B* rearranged tumors [7]. Recently, rare cases considered HG-ESS lacking *YWHAE*-rearrangement have been reported. These tumors were noted to have morphologic features resembling myxoid leiomyosarcoma and recurrent *ZC3H7B-BCOR* gene fusions [17].

We therefore now describe a case series of *YWHAE*-rearranged HG-ESS and their multimodal clinical management from two large cancer centers to begin to define the clinical management and outcomes of women with this recently defined disease. For each case treated with systemic therapy, an anthracycline-based regimen at any line of therapy resulted in a high response rate and, in two cases, complete radiologic response. Combination gemcitabine and docetaxel was also found to be effective as first-line therapy in one patient.

2. Methods

Institutional Review Board approval was obtained at the Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center to conduct this study. A retrospective search of all patients diagnosed with *YWHAE*-rearranged HG-ESS from 2012 to 2015 was undertaken. *YWHAE*-rearrangement testing was performed in six of the seven identified cases when initial pathology review raised suspicion for this diagnosis based on morphology and immunohistochemical features [5]. From review of our clinical database, one additional case was identified through retesting of archival tissue for *YWHAE*-rearrangement. Pathology slides and reports were retrospectively reviewed by two gynecologic pathologists and *t*(10;17)(q22;p13) *YWHAE* rearrangement confirmed by cytogenetics or fluorescence in-situ hybridization (FISH) with break-apart probes flanking the *YWHAE* gene. Patients who presented only for consultation or were lost to follow-up were excluded. Electronic medical records were reviewed for the date of diagnosis, stage at diagnosis, immunohistochemical and molecular pathology testing, surgical interventions, radiation treatments, chemotherapy regimens and response to treatment. Cancer stage was assigned based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria [18]. Response to treatment on imaging for patients with measurable disease was determined by radiographic images and radiology reports. Tumor response was determined as per RECIST [19]. Overall survival (OS) was defined as the interval from the date of diagnosis to date of death. Time to progression (TTP) for patients being treated with measurable disease was defined as the interval from the beginning of systemic therapy to evidence of disease progression on imaging studies.

3. Results

3.1. Patient characteristics and initial treatment

We identified 7 patients with *YWHAE*-rearranged HG-ESS who received treatment and follow-up at one of the two institutions. The patients ranged in age from 42 to 47 years. One (Case-7) underwent supracervical hysterectomy with morcellation at an outside institution prior to presenting at one of the study institutions, with subsequent diagnosis of FIGO Stage I *YWHAE*-rearranged HG-ESS. All other patients underwent hysterectomy without morcellation, and salpingo-oophorectomy was performed at the time of initial surgery or at a later date. Most patients (5/7) presented with FIGO Stage IIIB or higher. Histologically, tumors contained areas exhibiting characteristic round cell morphology with brisk mitotic activity that diffusely expressed cyclin D1; all were found to harbor the *YWHAE*-rearrangement by FISH or cytogenetics (Table 1). Two patients with ER/PR-positive disease were treated

Table 1
Patient characteristics, diagnosis and outcomes in *YWHAE*-rearranged HG-ESS. IHC: Immunohistochemistry; FIGO: International Federation of Gynecology and Obstetrics. The dash in the overall survival column indicates the patient is alive and under observation or treatment for disease.

Case	Age at diagnosis	*t*(10;17) diagnostic method	FIGO stage at diagnosis	Time from initial resection to metastasis (months)	Sites of metastasis at time of chemotherapy	Overall survival (months)
Case-1	44	FISH	IVB	–	Peritoneum	–
Case-2	45	FISH	IVB	–	Pelvis, liver, lung, pleura	–
Case-3	46	FISH	IVB	–	Abdomen, lymph node	33
Case-4	47	FISH	II	–	–	–
Case-5	46	FISH	IVB	–	Adnexa, lymph node, bone	–
Case-6	45	Cytogenetics	IIIB	65	Abdomen, pelvis	100
Case-7	42	FISH	I	64	Lung, mediastinum, abdomen, pelvis, lymph nodes, bone	123

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