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Case report

Prolonged response to exemestane following multiple surgical resections and hormonal therapies in a patient with recurrent endometrial stromal sarcoma

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ABSTRACT

Background: Endometrial stromal sarcomas (ESSs) are rare, indolent tumors with high recurrence rates. Management includes surgery and hormonal therapy given high estrogen and progesterone receptor (ER/PR) expression.
Case: A pre-menopausal patient with stage II ESSs (ER+/PR+) underwent primary surgery followed by adjuvant megestrol. Recurrence in the bladder/upper vagina (ER+/PR−) was diagnosed one year later and treated with anterior pelvic exenteration and adjuvant letrozole. Two years later she recurred and was treated with radical surgery and adjuvant exemestane therapy (tumor ER strongly +/PR+). The patient then had a five-year disease free interval before being diagnosed with her third recurrence (ER+).
Conclusion: Exemestane treatment for ESSs can lead to a prolonged response, even in the setting of progression after prior aromatase inhibitor treatment.

1. Introduction

Endometrial stromal tumors represent a spectrum of histologies ranging from benign to malignant lesions. Based on the 2003 World Health Organization (WHO) guidelines, cytologic differentiation and lymphovascular/myometrial invasion are used to classify endometrial stromal tumors into three general categories: endometrial stromal nodule (ESN), a benign lesion, endometrial stromal sarcoma (ESS), a low-grade lesion, and undifferentiated endometrial sarcoma (UES), a frankly malignant lesion (Yoon et al., 2014). Historically, ESS was distinguished as either low-grade or high-grade; however, high-grade lesions are now considered UES (Yoon et al., 2014). ESS, in particular, is rare and comprises approximately 0.2% of all uterine cancers and 10–25% of all uterine sarcomas (Yoon et al., 2014; Rauh-Hain and del Carmen, 2013; El-Khalfaoui et al., 2014).

Though much of the data on ESS is based on small studies and case series, it is generally considered to be an indolent tumor that is resistant to chemotherapy yet prone to recurrence. Patients with ESS, however, have a better overall survival when compared to patients with other uterine sarcomas (El-Khalfaoui et al., 2014). Hysterectomy with bilateral oophorectomy is the cornerstone of treatment for early stage disease; the role of lymphadenectomy remains controversial. In young women with early stage disease, ovarian conservation may be an option (Rauh-Hain and del Carmen, 2013). ESS typically demonstrates an over-expression of estrogen (ER) and progesterone receptors (PR) (Rauh-Hain and del Carmen, 2013). Adjuvant hormonal treatment has been shown to reduce the risk of recurrence when used in patients with advanced stage disease as well as improved clinical outcomes in the setting of recurrence, however, data is currently lacking on the use of adjuvant hormonal therapy for early stage disease (Rauh-Hain and del Carmen, 2013; Amant et al., 2007; Sommeijer and Sjoquist, 2013; Mizuno et al., 2012).

Adjuvant hormonal therapy options include megestrol or medroxyprogesterone, gonadotropin releasing hormone analogs (GnRHs), and aromatase inhibitors (AIs). Exemestane, a type 1 steroidal irreversible AI, is well tolerated and has shown clinical benefit for hormonally sensitive tumors (Lindemann et al., 2014; Thanopoulou et al., 2014). Exemestane has been used most commonly in the setting of breast cancer treatment or chemoprevention, but has also been used in endometrial carcinoma and leiomyosarcoma (Lindemann et al., 2014; Thanopoulou et al., 2014; Dunn et al., 2013; Bliss et al., 2012).

There is no current consensus on the optimal adjuvant hormonal therapy for recurrent ESSs. We present a case of a prolonged response to exemestane therapy in a patient with multiple recurrences of ESSs.

2. Case

A premenopausal patient with a benign pre-operative endometrial biopsy underwent a total abdominal hysterectomy and left salpingo-oophorectomy for menorrhagia. The uterus was found to have an ESS

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involving the deep myometrium, parametria, and cervix. She then underwent a right salpingo-oophorectomy and pelvic lymph node dissection with final pathology demonstrating a stage IIB endometrial stromal sarcoma (ER+/PR+). The patient was then started on adjuvant megestrol therapy.

One year later the patient presented with hematuria. Imaging studies demonstrated bladder and endovaginal masses. She underwent a supralevator anterior pelvic exenteration with ileal conduit urinary diversion. Final pathology demonstrated ESS (ER+/PR-), and she was treated with adjuvant letrozole.

Two years after the exenteration, a surveillance CT scan demonstrated an intravascular mass extending from the common iliac veins cephalad into the right atrium and ventricle (Figs. 1 and 2). The patient then underwent a multidisciplinary procedure with cardiothoracic surgery, vascular surgery, and urology. A median sternotomy and laparotomy was performed for exposure, and full cardiopulmonary bypass with deep hypothermic circulatory arrest (DHCA, 18°°C) was employed for approximately 30 min to allow removal of the intracardiac and retrohepatic tumor. During rewarming after the DHCA, the infrarenal IVC and left iliac system was opened longitudinally to remove the tumor. The abdominal portion of the sarcoma was >20 cm long and nearly obliterated the entire left iliac and IVC lumens. The pathology from the specimens revealed ESS (ER strongly +/PR +). The patient then began adjuvant exemestane therapy.

The patient remained disease-free for five years until routine surveillance imaging showed evidence of recurrence with masses in her ileal conduit and peritoneal cavity. She underwent an exploratory laparotomy, debulking, small bowel resection, and resection of the ileal conduit with creation of a new ileal conduit. The pathology was consistent with ESS recurrence (ER+). Her hormonal therapy was changed to anastrozole, which she continues today.

3. Discussion

Endometrial stromal sarcomas are the least common type of uterine neoplasm. Much of the current data on treatment management is limited to small case series. The mainstay for early stage disease consists of hysterectomy and bilateral oophorectomy. Adjuvant treatment usually consists of indefinite hormonal therapy as these indolent tumors are typically ER/PR positive. Adjuvant treatment with chemotherapy or radiation is not routinely recommended unless hormonal therapies have become ineffective (Amant et al., 2014).

Given the high rate of ER/PR expression in ESSs, reported as high as 100%, hormonal therapy has been advocated as first line treatment (Amant et al., 2014). Hormonal therapies used in the treatment of ESSs include megestrol or medroxyprogesterone, the GnRHs and the

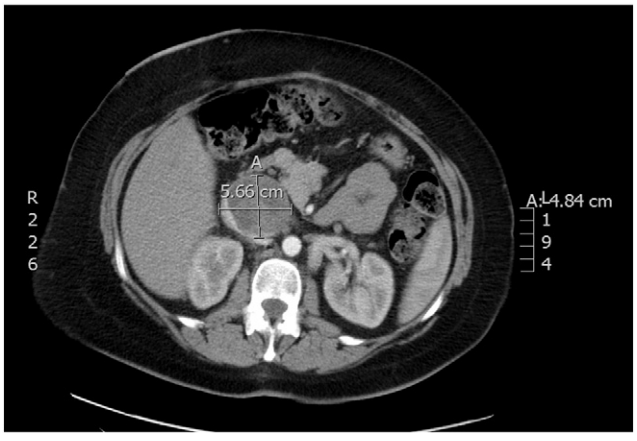

Fig. 1. CT scan demonstrating near-complete occlusion and marked distention of inferior vena cava.

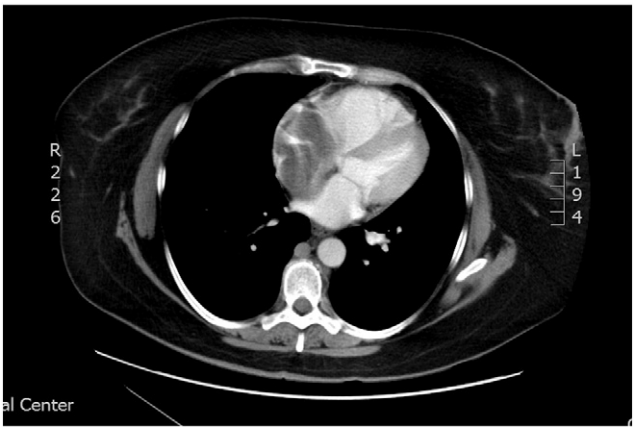

Fig. 2. CT scan showing large soft tissue mass filling and distending the right atrium.

AIs. There is little objective data on the most effective hormonal treatment regimen, dose, and duration of therapy.

Aromatase inhibitors have shown clinical benefit in ESSs although data is limited to case reports and small case series. Aromatase inhibitors block the synthesis of estrogen in peripheral adipose tissue, and directly inhibit aromatase activity in tumor tissue (Thanopoulou et al., 2014). There are two categories of AIs based on their chemical structure: type I AIs are steroidal inhibitors and bind aromatase irreversibly by covalent bonds, while type II AIs are nonsteroidal inhibitors that bind reversibly and covalently with aromatase (Chan and Fan, 2013). Exemestane is a type I AI whereas letrozole and anastrozole are type II AIs. Much of the knowledge gained from the clinical benefit of aromatase inhibitors comes from its use in breast cancer, however, there is little data comparing the two classes of AIs as there has been no head-to-head comparison of the two classes. Anastrozole, letrozole, and exemestane have all been shown to suppress estrogen by greater than 97%, however, potentially small variations in the level of estrogen suppression between the two classes of AIs may have some biological importance in length of response to one class versus the other (Dowsett, 1999). Additionally biologically significant differences in estrogen concentrations with treatment are likely below the threshold of standard immunoassay detection methods at present, and difficult to confirm as a result (Dowsett, 1999). Given the rarity of ESSs, the results from letrozole and anastrozole treatment have often been reported together, and both have demonstrated clinical benefits when used in hormone receptor positive uterine cancers (Thanopoulou et al., 2014). One small retrospective case series reported an overall response rate of 67% (60% partial response rate, 7% complete response rate), and a 20% stable disease rate in 16 patients with ESS treated with AIs (Altman et al., 2012). Additionally, these medications have demonstrated a lack of complete cross-resistance to each other when used to treat hormonally sensitive breast cancer though the etiology of this phenomenon has yet to be found (Lønning, 2009).

Treatment of ESS with exemestane has only been reported twice previously (Dowsett, 1999; Klaritsch et al., 2006); our case further demonstrates the therapeutic potential of exemestane for ESSs. Our patient with multiple ESS recurrences was without evidence of disease for 5 years with exemestane therapy. This case highlights two points regarding treatment of ESSs. First, when surgically feasible, resection of recurrent disease should be considered. This patient underwent three radical procedures over the 10 years since her original diagnosis, with each surgery resulting in complete resection. Each recurrence proved to be in a different location than the last, and this further emphasizes the effectiveness of surgery. The second point highlights the importance of continuing different AI therapy despite failure of prior AIs in tumors that are ER+. Whether radical debulking surgeries or the use of hormonal therapy contributes to better outcomes is unknown, however, it is plausible that a combination of both is necessary for a durable

response. As third-line therapy, it is notable that the patient experienced a five-year disease-free interval when using exemestane while prior hormonal treatments yielded 1–2 years. The lack of cross-resistance between different AIs allows an additional therapeutic window for treatment of ESSs with this class of medications. Although considered indolent, recurrent ESSs can be a challenging disease to treat requiring multidisciplinary surgical procedures and multiple hormonal therapies.

Conflict of interest statement

The author(s) declare that there are no conflicts of interest. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Walter Reed National Military Medical Center, the U.S. Air Force, the Department of the Army, Department of Defense, or the U.S. Government.

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