Gynecologic Oncology Reports 10 (2014) 30–31

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gore

Breast cancer in the setting of fertility-sparing treatment for endometrial cancer

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ARTICLE INFO

Article history:
Received 20 August 2014
Accepted 9 October 2014
Available online 27 October 2014

Keywords:
Endometrial cancer
Hormonal therapy
Fertility-sparing
Breast cancer

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States. With the growing obesity epidemic, an increasing number of women are diagnosed prior to menopause when fertility is desired (Gallup and Stock, 1984; Kim et al., 2013). While hysterectomy and bilateral salpingo-oophorectomy are standard of care, multiple studies have described the feasibility and safety of treating atypical endometrial hyperplasia and low grade carcinoma with high dose progestin therapy (Wang et al., 2014; Simpson et al., 2014). Progesterone therapy for endometrial neoplasia has been reported to commonly cause hyperglycemia, hypertension, nausea, vomiting, weight gain, and sexual dysfunction, but can also cause more serious reactions including pulmonary embolus, diabetes, adrenal suppression and cardiomyopathy (Thigpen et al., 1999). Progesterone is also known to increase the risk of breast cancer in women undergoing hormonal replacement therapy (Manson et al., 2013; Beral and Million Women Study Collaborators, 2003), however, breast cancer in a woman undergoing hormonal treatment for endometrial cancer has not been described. Here we report a case of advanced breast cancer in a 32 year old woman who had undergone hormonal therapy for fertility sparing treatment of endometrial cancer.

Case report

A 32 year old nulliparous woman with morbid obesity (body mass index 39.7) presented with heavy vaginal bleeding. Endometrial sampling demonstrated endometrioid endometrial adenocarcinoma, FIGO grade 1. Magnetic resonance imaging showed no evidence of myometrial invasion or extrauterine disease. Her family history was significant for two aunts with breast cancer. The patient was recommended surgical treatment with hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection as standard of care, but desired fertility preservation and elected a trial of conservative management. She was enrolled on a clinical trial that prescribed megestrol acetate, 160 mg daily. She was offered genetic and nutritional counseling but declined.

The patient underwent regular endometrial sampling and demonstrated a complete response by dilatation and curettage after 14 months of treatment. She desired immediate fertility and was referred to reproductive endocrinology to expedite pregnancy, with sampling recommended at six months interval if fertility was not achieved. She represented one year later not having become pregnant and a surveillance biopsy demonstrated recurrent FIGO grade 1 endometrial cancer. At this visit she also reported irregular vaginal spotting. The patient was again recommended standard of care surgical management and weight loss strategies but declined and resumed megestrol acetate. Nine months later she had complete resolution of disease on a dilation and curettage specimen. She returned for fertility treatment, but did not become pregnant and a surveillance biopsy 8 months later demonstrated complex hyperplasia without atypia. The patient elected to restart megestrol acetate, however after just 4 weeks reported bothersome abdominal pain and nausea. The systemic progesterone was discontinued and a progesterone-releasing intrauterine device (IUD) was placed. The patient was seen four weeks later and reported right breast pain. On physical exam and imaging she was found to have a 5 cm irregular mass with enlarged right axillary lymph nodes. A breast biopsy demonstrated poorly differentiated invasive ductal carcinoma that was estrogen and progesterone receptor positive. An axillary lymph node fine needle aspiration revealed malignant cell consistent with stage cT3N1 breast cancer.

An interdisciplinary meeting was called with the patient's medical, surgical and gynecologic oncology teams. The consensus plan was to treat the breast cancer while keeping the IUD in place and then proceed with hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection. She received neoadjuvant adriamycin, cyclophosphamide,

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http://dx.doi.org/10.1016/j.gore.2014.10.002

and paclitaxel. Subsequent imaging studies revealed a poor response to chemotherapy with new dermal involvement. She underwent a bilateral mastectomy and axillary lymph node dissection and on final pathology had involvement of multiple axillary lymph nodes She received postoperative radiation therapy. The patient's menses ceased with chemotherapy, she has not had additional bleeding and the most recent endometrial sampling demonstrated complete resolution of disease. The patient plans to undergo Letrozole-triggered oocyte retrieval and will then undergo definitive surgical management for her endometrial cancer.

Discussion

While the average age of diagnosis of endometrial cancer is 61, 25% of cases occur in pre-menopausal women and 3–5% of new cases occur in women 40 years or younger (Gallup and Stock, 1984). The standard treatment for endometrial carcinoma is total extra-fascial hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. However, premenopausal women with endometrial carcinoma often desire maintenance of fertility and multiple studies support progesterone therapy as a safe and effective treatment for endometrial hyperplasia and low grade carcinoma (Wang et al., 2014; Simpson et al., 2014). In 2004, Ramirez et al. (2004) reported a response rate of 76% among patients with well differentiated endometrial carcinoma who were treated with progesterone. Additionally, a recent systematic review of forty-five studies demonstrated a 78% complete response rate (Gunderson et al., 2012).

Progesterone is a steroid hormone that is essential for coordinating normal female reproductive physiology. The effect of progesterone is known to differ by tissue type and location. While in the endometrium progesterone has a protective effect against estrogen-dependent carcinogenesis, in breast tissue it has a pro-proliferative role, expanding a stem cell population that is sensitive to transformation (Kim et al., 2013). Basic science research supports the role of progestins in breast tumorigenesis. Tissue samples from breast cancer specimens demonstrate an increased percentage of proliferating estrogen and progesterone receptor-positive cells (Kim et al., 2013). An overexpression of progesterone receptors has been observed in mice deficient in BRCA1 and p53, mutations known to be associated with increased risk of breast cancer. Furthermore, treatment of mutant mice with the progesterone antagonist mifepristone can prevent mammary tumorigenesis (Kim et al., 2013). Neubauer et al. (2011) incubated breast cancer cells with increasing estradiol concentrations and different progestins and found that medroxyprogesterone resulted in an increased proliferation of breast cancer cells.

This case is notable because treatment for one cancer may have resulted in a second cancer. While the association between progesterone and breast cancer is well recognized in the population of women receiving hormone replacement therapy, it has not been clearly established among young women undergoing medical treatment for endometrial cancer. When women elect to undergo treatment with progestins for conservative management of endometrial neoplasia, the counseling usually focuses on the risk of persistence or progression of the endometrial cancer. Of note, this patient had other risk factors for the development of breast cancer including family history of breast cancer, a possible undiagnosed familial cancer syndrome and obesity. Whether progestins, genetics, obesity or a combination of factors contributed to this cancer diagnosis remains unclear. Nevertheless, this case highlights the importance of thorough counseling prior to pursuing conservative management of endometrial cancer and further studies exploring the side effects of high dose progesterone in young women with endometrial cancer.

Conflict of interest statement

None of the authors have a conflict of interest to report.

Informed consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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