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Case series

Successful treatment of low-grade endometrial cancer in premenopausal women with an aromatase inhibitor after failure with oral or intrauterine progesterone

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A B S T R A C T

Introduction: Young women with endometrial intraepithelial hyperplasia or low-grade endometrial carcinoma are potential candidates for conservative fertility sparing therapy utilizing progesterone rather than hysterectomy. High-dose progesterone treatment is associated with 55–80% initial response but high relapse rates. Using aromatase inhibitors in conjunction with high-dose progesterone has largely been unstudied. Case descriptions: Three obese premenopausal women with endometrial cancer failed to respond to oral or intrauterine progesterone as first line therapy. Due to their desire to continue to pursue fertility sparing treatment options, an aromatase inhibitor was added to their treatment regimen. This resulted in resolution of their malignancy in each case. Discussion: In obese premenopausal women, the mechanism of malignant transformation in endometrial carcinoma is considered to be an association with relatively high levels of serum estrogen from peripheral conversion of androgens to estrone in adipose tissue with a deficiency in progesterone exposure due to chronic anovulation. Using aromatase inhibitors seems reasonable as an adjunct to progesterone given the high likelihood that this population has a significant proportion of their estrogen production coming from peripheral conversion in adipose tissue. This case series is unique in that each woman initially failed to respond to progesterone but had resolution when an aromatase inhibitor was added to their treatment regimen. This would suggest that obese women with low grade malignancy or hyperplasia who have no radiographic evidence of deep myometrial invasion, ovarian or retroperitoneal metastases and who wish to retain their fertility may be treated with intrauterine progesterone and an aromatase inhibitor.

1. Introduction

Endometrial carcinoma is the fourth most common malignancy in women in the United States. The Surveillance, Epidemiology, and End Results Program (SEER) estimates that 54,870 women will develop endometrial cancer in 2015 and 10,170 will die of the disease. They estimate a lifetime risk for the development of this malignancy at approximately 3%. This investigation also suggests that the incidence of endometrial cancer has slightly increased since 1986.(Garg and Soslow, 2014; American Cancer Society, 2015; Howlader et al., 1975) Most investigators theorize that this trend correlates with the increased incidence in obesity in US women, especially young women.(Garg and Soslow, 2014; American Cancer Society, 2015; Howlader et al., 1975) In women with endometrial cancer, the proportion of young women (age < 50) with malignancy also appears to be increasing. Wartko, using SEER data, evaluated 63,428 cases of endometrial cancer in the US from 1992 to 2009. Of these, 17% were less than age 50 and they reported that the proportion of women with uterine cancer who are young is likely increasing over time.(Wartko et al., 2013) Young women with endometrial intraepithelial hyperplasia (EIN) and low-grade malignancy are potential candidates for conservative fertility sparing therapy utilizing progesterone rather than hysterectomy. In such patients, high-dose progesterone treatment is associated with 55–80% initial complete response but high relapse rates (50%) over time likely secondary to poor compliance with long term use of high doses of progesterone.(Simpson et al., 2014; Pronin et al., n.d.; Wang et al., 2014) Some investigations suggest that intra-uterine progesterone treatment may be more effective than oral therapy especially in women with hyperplasia.(Kim et al., 2012; Orbo et al., 2014) In women who respond to progesterone, there is a low rate of live births.(Simpson et al., 2014; Pronin et al., n.d.) Pregnancy rates do appear to be better when assisted reproductive technologies are employed.(Fujimoto et al., 2014) Finally, the use of aromatase inhibitors in conjunction with high-dose progesterone treatment has largely been unstudied. The following

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Table 1
Description of each case with their treatment regimen and subsequent biopsy. (MA is megestrol acetate, Bx = biopsy, EC = endometrial carcinoma).

Case number	Initial biopsy	Initial treatment	Second biopsy	2nd treatment	Third biopsy	3rd treatment	Fourth biopsy	Outcomes
1	Grade I endometriod endometrial carcinoma	160 mg/day MA × 6 months	Atypical hyperplasia	160 mg/day MA + anastrozole 1 mg/day × 6 months	Neg for cancer	N/A	N/A	10 months following this, Bx showed recurrent EC, underwent hysterectomy
2	Grade I endometriod endometrial carcinoma	160 mg/day MA × 6 months	Grade I endometriod endometrial cancer	160 mg/day MA + anastrozole 1 mg/day × 6 months	Persistent grade I EC	IUD supplement for oral progestin × 8 months	Neg for cancer	4 months later, bx showed recurrent EC, planning for hysterectomy
3	Grade II-III endometriod endometrial carcinoma	160 mg/day MA × 6 months	Grade III endometriod endometrial cancer	Progestin IUD × 8 months	Grade III endometriod endometrial cancer	Progestin IUD anastrozole 1 mg/day × 7 months	Neg for cancer	7 months later, bx showed recurrent EC, planning for hysterectomy

is a report of four obese premenopausal women with endometrial cancer who failed to respond to oral or intrauterine progesterone as first line therapy but had resolution of their malignancy when aromatase inhibitors were added to their treatment regimen. (See Table 1.)

2. Case reports

2.1. Case one

RO is a 32-year old nulligravida woman with a BMI of 38 who underwent dilatation and uterine curettage for evaluation of menorrhagia which revealed a grade I endometriod endometrial carcinoma. She elected to undergo fertility-sparing therapy for her malignancy and was treated with megestrol acetate 160 mg/day orally for 6 months. Prior to progesterone therapy she had a pelvic magnetic resonance imaging (MRI) scan which revealed no myometrial invasion of her tumor, normal appearing ovaries, and no evidence of retroperitoneal adenopathy. Repeat D & C revealed persistent atypical hyperplasia. 1 mg daily of oral anastrozole was added to her hormone treatment plan for six months. Subsequent D & C showed normal endometrium. She was referred for reproductive endocrinology (REI) consultation and was given cyclic provera 10 mg/daily by mouth for 10 days of each month. She also underwent attempts at glucose control in preparation of ovulation induction and subsequently underwent repeat endometrial biopsy which revealed a grade I malignancy. She was advised to undergo hysterectomy and oophorectomy. This was performed and her pathology showed a type I, grade 1, stage IA (tumor confined to the endometrium) malignancy. She was felt to be at low risk for recurrence and did not receive postoperative adjuvant therapy. She remains free of disease three months after surgery.

2.2. Case two

DO is a 28-year old nulligravida woman with a BMI of 47 who underwent endometrial biopsy after developing menorrhagia which showed a grade I endometriod endometrial cancer. Subsequent MRI scan showed no myometrial invasion of tumor and no evidence of ovarian metastases or retroperitoneal adenopathy. She was treated with 160 mg/day of megestrol acetate for six months and subsequent D & C revealed persistent grade I cancer. She was then treated with megestrol acetate 160 mg/day plus anastrozole 1 mg/day for six months. Repeat D & C again showed persistent grade-I cancer. A progestin secreting intra-uterine device was placed and her oral progesterone was discontinued. Repeat D & C after eight months of treatment revealed normal endometrium with no evidence of malignancy. Four months later she was then referred to REI for consultation. Prior to ovulation induction, she underwent repeat endometrial biopsy that showed a grade I malignancy. She was advised to undergo hysterectomy but refused due to her desires for preserved fertility. A second progesterone containing IUD was placed and she was again started on oral anastrozole 1 mg/daily. Seven months later, she underwent a D & C with placement of a new IUD. Histology showed a grade II malignancy. She has been counseled on proceeding with surgical management for this with hysterectomy.

2.3. Case three

LV is a 36 year-old nulligravid Hispanic woman with a BMI of 42 who underwent endometrial biopsy for significant menorrhagia which was consistent with a grade II-III endometrial cancer. She refused hysterectomy and wished to pursue fertility sparing treatment. A pelvic MRI showed no evidence of retroperitoneal adenopathy, ovarian metastases or deep myometrial invasion. She was treated with oral megace 160 mg/day for six months. Repeat D & C revealed a grade III cancer and she was again advised to undergo hysterectomy which she refused. Repeat MRI was normal and she was treated with a progestin

containing IUD for eight months. Repeat D & C again revealed persistent grade II cancer. At that time, oral anastrozole (1 mg/day) was added to her treatment regimen. Repeat D & C after 7 months of treatment was normal. She was referred to REI for evaluation in hopes of attaining a pregnancy. As part of her workup, a repeat endometrial biopsy was performed that showed persistent cancer as defined as grade III. She has been counseled on proceeding with surgical management for her persistent disease.

3. Discussion

The vast majority of women with endometrial cancer are considered to have type I-malignancies (80%) that appears to be associated with exposure to high levels of endogenous or exogenous estrogens.(Garg and Soslow, 2014). Despite a high likelihood of cure with hysterectomy and surgical staging, young women often elect to undergo fertility-sparing treatment followed by evaluation for assisted reproductive technologies after resolution of their cancer. Exposure of hyperplastic or malignant endometrium to progesterone is associated with multiple histologic and translational events including inhibition of estrogen receptor expression, up-regulation of progesterone receptor A and B isoforms, induction of endometrial decidualization via cAMP signaling, and epigenetic mechanisms including microRNA expression which often lead to normalization of the endometrium.(Young, 2013).

Fertility-sparing treatment for appropriate candidates who have low-grade malignancies and radiographic features suggestive of early stage cancer have most commonly used oral progesterone at fairly high doses. Prior studies show fairly good success rates but also a significant potential for relapse. Newer and better-designed investigations indicate that intrauterine treatment with progesterone may be a more effective therapy. In Scandinavia, women with endometrial hyperplasia were randomized to oral versus intrauterine progesterone with resolution of hyperplasia in all women who received localized treatment (intrauterine).(Orbo et al., 2014). Therefore, it would seem reasonable to treat women with endometrial hyperplasia or low grade carcinoma with progesterone secreting devices within the uterine cavity as the first line therapy in women who do not want to undergo hysterectomy or who are poor surgical candidates.

In premenopausal women who are morbidly obese, the use of aromatase inhibitors seems reasonable as an adjunct to oral or intrauterine progesterone given the high likelihood that they have a significant proportion of their estrogen production coming from peripheral conversion in adipose tissue. There is some evidence to suggest efficacy of these agents both in in-vitro and clinical studies. Investigators in China exposed endometrial cancer cell lines to letrozole and everolimus, which resulted in inhibition of proliferation and an increase in apoptosis.(Liu et al., 2014) Thangavelu and colleagues performed a randomized trial in 16 women with endometrial cancer comparing aromatase inhibitors versus placebo and demonstrated reduction in expression of estrogen and androgen receptors as well as inhibition of cellular proliferation in those exposed to aromatase inhibitors compared to placebo.(Thanggavelu et al., 2013). Investigators treated a cohort of women with endometrial hyperplasia and cancer with aromatase inhibitors and demonstrated consistent reduction in endometrial thickness in exposed patients who were not felt to be good candidates for hysterectomy.(Agorastos et al., 2005). Finally, Burnett reported the efficacy of aromatase inhibitors in conjunction with oral progesterone as a treatment for endometrial cancer in two premenopausal women and showed resolution of the malignancy. (Burnett et al., 2004).

Our experience of treating three premenopausal women with low-grade endometrial cancer is unique in that they initially failed to respond to oral progesterone but had resolution when an aromatase inhibitor was added to their treatment regimen. Our experience, and review of the medical literature, would suggest that women with low grade malignancy or hyperplasia who have no radiographic evidence of deep myometrial invasion or ovarian or retroperitoneal metastases and who wish to retain their fertility may be treated with intrauterine progesterone and an aromatase inhibitor if they are obese. It is noteworthy to mention that each case did ultimately have relapse of their cancer which lead to either counseling of surgical management or actually undergoing surgery. This combination of medications could be investigated further with clinical trials.

Conflict of interest statement

We have no affiliation or involvement with any organization for financial or non-financial interest.

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