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Challenging Regimen for Long-Term Conservative Treatment of Endometrial Adenocarcinoma in Young Women: A Case Report and Review of the Literature

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Key Words

Endometrial adenocarcinoma · Polycystic ovary syndrome · Levonorgestrel intrauterine system

Abstract

A 20-year-old obese Thai woman with polycystic ovary syndrome and clinical stage I well-differentiated endometrial carcinoma denied surgical staging. Chest X-ray and magnetic resonance imaging of the whole abdomen suggested neither distance metastasis nor local invasion of the cancer. After 3 months of systemic progestin therapy with megestrol acetate (MA) 480 mg/day, the endometrial carcinoma persisted. The treatment was changed to a combination of levonorgestrel intrauterine system (LNG-IUS) and MA with a stepping-up from 160 to 480 mg/day. Complete remission was achieved at treatment month 9. Prevention of recurrence was provided using LNG-IUS plus MA 160 mg/day. Endometrial surveillance using trimonthly transvaginal ultrasonography and endometrial biopsy suggested no recurrence for at least 24 months after remission.

Introduction

Endometrial carcinoma is one of the most common gynecologic malignancies. Although it is primarily a disease of postmenopausal women, 25% of patients are in the premenopausal period, and 3–5% are <40 years of age [1–3]. Obesity and chronic anovulation are major risk factors of endometrial carcinoma in young women [4, 5]. These conditions are associated with unopposed estrogen status, which induces endometrium proliferation resulting in increased risks of endometrial hyperplasia and

carcinoma. The standard treatment of endometrial carcinoma is surgical staging, which would destroy the reproductive function. Alternatively, conservative treatment with high-dose progestin is feasible in young women who wish to retain their reproductive function [3, 6–9], as cancers in these women are usually well-differentiated and in an early stage at the time of diagnosis [1, 10]. Unfortunately, some reports showed that obese patients may not optimally respond to either systemic or local progestin therapy [11, 12], but a combination of both therapies may intensify the therapeutic effect [13]. In this report, we present a case of clinical stage I well-differentiated endometrial carcinoma in an obese, young Thai woman with polycystic ovary syndrome (PCOS) treated with a combination of levonorgestrel intrauterine system (LNG-IUS) and an oral progestin, megestrol acetate (MA).

Case Report

A 20-year-old Thai woman presented with oligomenorrhea since menarche. Her last menstrual period had occurred 2 months prior to the visit to our clinic. She had never been on treatment for her menstrual abnormality. She denied having had any medical diseases. She was obese (body mass index of 28.7 measured in kg/m²) with central obesity (waist circumference of 100 cm). She had normotensive blood pressure and acanthosis nigricans, but she had no clinical hyperandrogenism. Ultrasonography demonstrated polycystic ovaries, a normal-sized uterus and hyperechoic endometrium with a thickness of 19.8 mm. Blood tests for prolactin, thyroid-stimulating hormone, cortisol, dehydroepiandrosterone sulphate, and free testosterone were within normal limits. She had insulin resistance (homeostatic measurement assessment-insulin resistance; HOMA-IR = 3.60) but no other metabolic derangements. She was diagnosed of PCOS according to the revised 2003 Rotterdam criteria [14].

Sonohysterography was performed to investigate the suspected intrauterine lesion, and it revealed a polypoid mass of 1.99 × 1.31 cm in diameter. Hysteroscopy showed a polyp protruding from the fundal part of the uterine cavity. The mass was totally removed using an electrical loop. Histopathological report revealed a well-differentiated endometrioid adenocarcinoma arising in the context of atypical complex endometrial hyperplasia.

The patient denied surgical staging for endometrial carcinoma. A chest X-ray and magnetic resonance imaging (MRI) were used to estimate the extent of the cancer. The images revealed no myometrial invasion, no extrauterine spreading, no enlarged pelvic or para-aortic lymph nodes, and no liver metastasis. The information suggested clinical stage I disease. The patient was informed about diagnosis and prognosis. Treatment options were discussed. She chose conservative medical treatment, although being aware that it was not the standard treatment.

The patient was advised to practice lifestyle modification to reduce her weight. She was treated with MA 480 mg/day. Treatment response was evaluated using uterine curettage every 3 months. In spite of side effects, including bloating and increasing appetite, the patient agreed to continue this treatment regimen. By the end of treatment month 3, uterine curettage was performed and histopathology of endometrium still showed a well-differentiated adenocarcinoma and atypical complex hyperplasia. Nevertheless, the patient insisted to continue conservative treatment but asked for a treatment option with fewer side effects. She agreed to use a combination of LNG-IUS and a lower MA dose of 160 mg/day. Endometrial biopsy was performed using a disposable endometrial cell sampler (Endocel®, Wallach Surgical Devices, Inc.) at the end of treatment months 3 and 6. Histopathology of the endometrium of the former revealed an inactive endometrial gland with pseudodecidual change, but the latter revealed a tiny fragment of cytologic glandular atypia and multiple fragments of inactive endometrium. The dose of MA was increased to 480 mg/day. Three months later the LNG-IUS was removed and uterine curettage was performed under general anesthesia. Histopathology of the endometrium revealed scattered small fragments of inactive epithelium, pseudodecidual change of stroma, without hyperplasia or endometrial carcinoma. A new LNG-IUS was inserted and the MA dose was reduced to 160 mg/day. The patient could better tolerate this treatment regimen. We planned to monitor her with trimonthly ultrasonography and endometrial biopsy. There was no recurrence for at least 24 months after the last endometrial surveillance, which did not show any malignant endometrial cell.

Discussion

Decision to choose conservative treatment for endometrial carcinoma needs adequate information, such as cellular grading, evidence of myometrial invasion and extrauterine spreading, and contraindications for medication. Moreover, patients have to be informed that the conservative treatment is not the standard treatment for this disease [3].

Oral progestin therapy is the first choice of conservative treatment. Medroxyprogesterone acetate (MPA) and MA are the two most commonly used oral progestins. The optimal dosage is yet inconclusive. The Gynecologic Oncology Group states that MPA 200 mg/day is an effective dose [7]; however, a dose up to 600 mg/day has been reported [3]. MA 40–160 mg/day is the most frequently used medical treatment in the USA [15–17]. The aforementioned oral progestin therapy had a complete response rate varying from 62 to 76% and a time to complete response from 3 to 9 months [3, 17, 18]. A higher dose of oral progestin has intolerable systemic side effects, and there is no evidence of higher effectiveness.

Local application of progestogen is another conservative therapeutic measure. Montz et al. [19] were the first to report that progesterone-intrauterine device (IUD) provided a complete response rate of 75% at the end of treatment month 12. Unfortunately, this progesterone-IUD is no longer commercially available. A novel progestin-medicated IUD, LNG-IUS, was shown to be effective for the prevention of endometrial hyperplasia in postmenopausal hormone therapy [20–22] and for the treatment of endometrial hyperplasia with or without atypia [23–25]. At present, 7 cases of endometrial carcinoma treated with LNG-IUS have been reported as summarized in [table 1](#); 2 cases had complete response 5–6 months after insertion of the IUS, whereas 4 cases with persistent cancer had hysterectomy and the specimens showed myometrial invasion [11–13]. It is likely that the non-response to progestin therapy, either to local [11, 12] or oral [6] regimens, might be due to the pre-existing myometrial invasion. There is evidence that transvaginal ultrasonography and MRI may be promising tools for the evaluation of myometrial invasion [26, 27], therefore these tools would be valuable in case selection for conservative treatment.

In the present case report, the patient was very young and wanted to preserve her fertility potential. Conservative treatment with progestin was considered. After high-dose oral MA (480 mg/day) treatment for 3 months, the endometrial carcinoma still existed. Since a higher dose of MA was not tolerable and had no evidence of more effectiveness, a combination of LNG-IUS and oral MA was provided. This combined treatment would theoretically deliver a higher dose of progestin to the endometrial tissue, but with less systemic side effects. An impressive response was observed with this combined treatment in our patient as the lesion was clear at treatment month 3. However, endometrial biopsy at treatment month 6 revealed a tiny fragment of cytological glandular atypia. Possibly, the endometrial biopsy performed at treatment month 3 had failed to detect the presumably persistent lesion. A meta-analysis shows that the sensitivity of endometrial biopsy to detect endometrial carcinoma is approximately 90% [28]. Therefore, the negative biopsy in this high-risk patient indicated the need of a more sensitive diagnostic tool such as endometrial curettage or hysteroscopy. In the present case, after increasing the MA dose to 480 mg/day in combination with LNG-IUS, histopathology of uterine curettage showed neither hyperplasia nor endometrial carcinoma. This was the first report of successful treatment of endometrial carcinoma using the combination of LNG-

IUS and MA. Moreover, our patient was the youngest compared with the cases in previous reports as summarized in [table 1](#). Long-term management is therefore the challenging issue.

The histological regression of the endometrial carcinoma in our patient was very encouraging. Although there exist several case reports of endometrial adenocarcinoma following the insertion of a LNG-IUS [29, 30], the combination of systemic progestin and LNG-IUS may decrease this concern. Even though patients can achieve complete response with conservative medical treatment, at least one third of them have recurrence by 20 months after cessation of treatments [3]. Therefore, prevention of recurrence is necessary. Potential preventive treatments include oral contraception, and cyclic or continuous progestins [3, 6]. In our patient, we continued the combination of LNG-IUS and oral progestin but with lower MA dosage (160 mg/day); this regimen has proved effective for 24 months until now. Optimal monitoring is yet unknown. A holistic approach for other problems such as obesity, metabolic abnormality, and infertility should also be ensured for this patient.

In conclusion, this was the first report of successful conservative treatment of endometrial carcinoma in a very young, obese Asian woman using the combination of LNG-IUS plus oral MA. This regimen is promising for both treatment and prevention of recurrence. We hope that our report will give a significant contribution to this issue.

Acknowledgement

We thank all staff members of the Gynecologic Endocrinology Unit who took good care of the patient.

Table 1. Summary of reported cases of endometrial carcinoma treated with progesterone-IUD or LNG-IUS

Author year reference	No. of cases	Age years	Associated condition	Presenting symptom	Clinical staging/initial histology	Treatment	Follow-up response
Montz et al., 2002 [19]	1–12				endometrioid carcinoma stage I, grade 1	Progestasert®	7 of 11 cases showed negative malignant endometrial cells at treatment month 6. 6 of 8 cases showed negative malignant endometrial cells at treatment month 12
Bahamondes et al., 2003 [12]	1	31	morbid obesity	menorrhagia	endometrial carcinoma stage I, grade 1	LNG-IUS	7 months after insertion, pathological report of radical hysterectomy revealed grade 1 endometrioid carcinoma restricted to the endometrial mucosa
	2	62	morbid obesity	postmenopausal bleeding	endometrial carcinoma stage I, grade 1	LNG-IUS	6 months after insertion, pathological report of radical hysterectomy revealed grade 1 mixed endometrioid and mucinous well-differentiated adenocarcinoma with invasion of half of the myometrium
Giannopoulos et al., 2004 [13]	1	78	Morbid obesity, hypertension, coronary artery disease	postmenopausal bleeding	endometrial adenocarcinoma background of atypical hyperplasia stage I, grade 1	LNG-IUS and MPA 400 mg/day	Predominantly pseudodecidualised stroma with small inactive glands at treatment month 5
Dhar et al., 2005 [11]	1	64	obesity, diabetes mellitus	postmenopausal bleeding	endometrial adenocarcinoma background of atypical hyperplasia/stage I, grade 1	LNG-IUS	Inactive endometrium at treatment month 6 and remission at treatment month 36
	2	73	obesity, diabetes mellitus, chronic lymphatic leukemia	postmenopausal bleeding	endometrial adenocarcinoma background of atypical hyperplasia/stage I, grade 1	LNG-IUS	Hysterectomy was performed (at treatment month 6 after insertion) due to persistence of bleeding, histopathological report still showed grade 1 endometrial adenocarcinoma
	3	80	obesity, diabetes mellitus, multiple cardiovascular accident	postmenopausal bleeding	endometrial adenocarcinoma stage I, grade 1	LNG-IUS	Intermittent symptom, died of pneumonia at month 24 after insertion
	4	73	obesity, diabetes mellitus, aortic stenosis, left brachial embolectomy	postmenopausal bleeding	endometrial adenocarcinoma stage I, grade 1	LNG-IUS	Persistent of diseases at treatment month 18, histopathological report still showed endometrioid adenocarcinoma

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