Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases

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Summary

Two women with endometrial carcinoma who wished to preserve their childbearing ability received conservative treatment by medroxyprogesterone acetate (MPA, 600 mg/day for 22 weeks and 29 weeks, respectively). Following regression of endometrial lesions, their infertility was treated by inducing ovulation. Intact pregnancy was diagnosed 13 months and 11 months after completion of the MPA treatment, respectively. One patient had a twin pregnancy and delivered two infants at 35 weeks of gestational age. The other patient delivered a full-term baby. They had no evidence of recurrence 60 months and 31 months after the conservative treatment, respectively. We believe this conservative treatment with progestin may be safely performed for young patients with endometrial cancer who wish to preserve their fertility.

Key words: Endometrial carcinoma; Conservative therapy; Progestin; Fertility.

Introduction

Endometrial carcinoma is the second frequent malignant tumor of the female genital tract and its incidence has been increasing steadily in Japan [1]. Many patients with endometrial carcinoma are in their 50's and only 2.9 to 14.4% of them are under age 40 [2-4]. Although standard treatment of endometrial cancer consists of hysterectomy and bilateral salpingo-oophorectomy, young patients during reproductive years are deprived of their capability of childbearing.

Gusberg [5] reviewed that carcinogenesis in endometrial carcinoma seems to be highly hormone dependent at least for the majority of endometrial cancer in young women. Prolonged unopposed estrogen exposure in infertile patients may induce endometrial hyperplasia progressing to carcinoma. From these observations, it is considered that well-differentiated early endometrial cancer in selected patients may be controlled by progestins alone [6-9]. We report on the conservative treatment of endometrial cancer in two young infertile women followed by two pregnancies achieved by induction of ovulation.

Case Report

Case 1

A 34-year-old Japanese woman, nulligravida, had a history of unovulatory cycles and primary infertility for 2 years. There was no history of abnormal genital bleeding. Laparoscopic examination at a nearby hospital revealed a polycystic ovary, and endometrial biopsy performed on September 16, 1994 revealed endometrial complex hyperplasia. She was followed-up until March 29, 1995 when dilatation and curettage produced a diagnosis of endometrial adenocarcinoma. The patient was referred to Kitasato University Hospital for further examination on April 12, 1995. Pelvic examination revealed no abnormal findings in the uterus and ovaries and her cervix appeared healthy. The Pap cervical smear was negative. Endometrial smear obtained by using Endocyte, however, was positive for possible adenocanthoma. A fractional curettage showed endometrial adenocarcinoma without cervical invasion. Hysteroscopic examination was performed under general anesthesia and papillary lesions with easy bleeding were observed in the entire uterine cavity. Tissue sample of the endometrial curettings showed well-differentiated endometrioid adenocarcinoma concomitant with endometrial hyperplasia (Fig. 1). Squamous metaplasia was seen in the small area. Estrogen receptor and progesterone receptor in the endometrial tissue measured by the radio-receptor assay were 22.7 fmol/mg protein and 121.0 fmol/mg protein, respectively.

MRI confirmed the thick endometrial layer and the absence of myometrial invasion and cervical involvement. A CT scan of the abdomen and pelvis, chest X-ray, cystoscopy and Barium-enema disclosed no extrauterine disease. The patient was diagnosed with G1 endometrial carcinoma, clinical stage I, and was started on continuous oral medroxyprogesterone acetate (MPA), 600 mg/day, on June 2, 1995 till January 21, 1996, after having a detailed informed consent on progestin therapy. During the treatment, an endometrial biopsy was performed every two weeks. Endometrial sample after two weeks of therapy revealed a decrease in the number of endometrial glands and lowered nuclear/cytoplasmic ratio with a decrease in nuclear chromatin staining of the glandular cells (Fig. 2). Endometrial stroma was observed to be edematous. Decidual change in the stroma and atrophic endometrial glands were evident after six weeks of therapy. Atrophic endometrial glands with squamous metaplasia were observed in the histological specimen after 20 weeks of therapy (Fig. 3). On November 10, 1995 (22 weeks of MPA therapy), hysteroscopy visualized a smooth and atrophic surface of the entire cavity. No endometrial tissue could be obtained. The total dose of MPA was 134,400 mg. In order to prevent prolonged exposure to estrogens, cyclic MPA therapy, which consisted of 10 mg daily for 14 consecutive days, followed by 14 non-prescription days was additionally given. From October 1996 ovarian stimulation was performed

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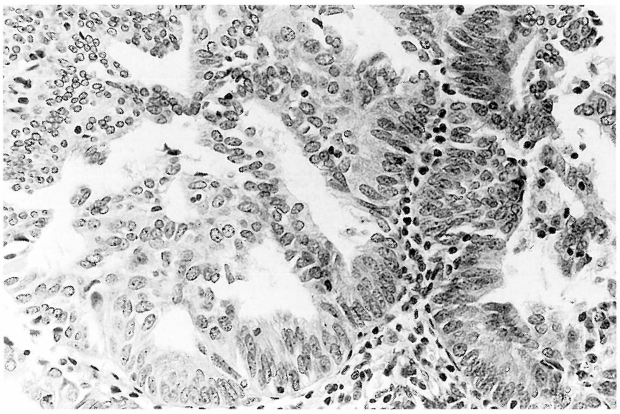

Figure 1. — Case 1. A well-differentiated adenocarcinoma showing proliferating neoplastic glands with crowded epithelial cells. (H & E, 5 x 20).

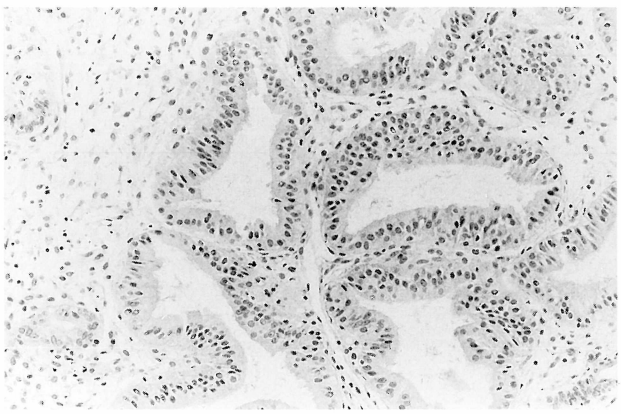

Figure 2. — Case 1. Two weeks after treatment with MPA, decreased nuclear/cytoplasmic ratio and edematous stromal reaction. (H & E, 5 x 10).

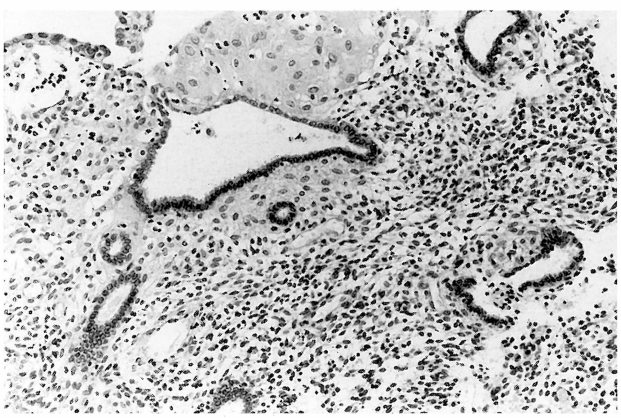

Figure 3. — Case 1. Twenty weeks after treatment with MPA, an endometrium with atrophic glands lined by small cells and squamous metaplasia. (H & E, 5 x 10).

to induce ovulation with clomiphen citrate followed by follicle-stimulating hormone (FSH) and human chorionic gonadotropin (HCG) according to standard protocols. The first ovulation was confirmed by basal body temperature on January 13, 1998 after unsuccessful induction for 11 months and artificial insemination was added. On February 16, 1998 ultrasound revealed a twin pregnancy. In the second trimester she was managed with

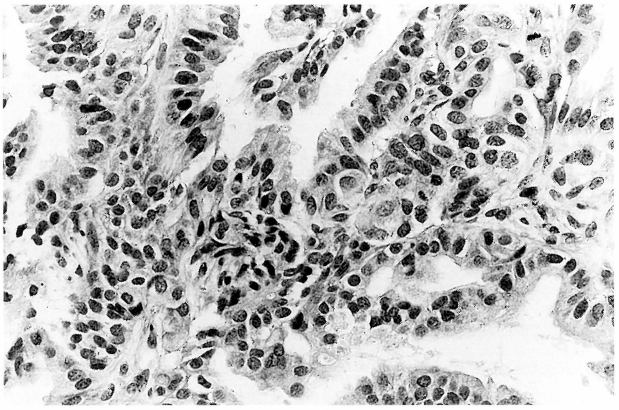

Figure 4. — Case 2. A well-differentiated adenocarcinoma showing pleomorphic nuclei and mitotic activity. (H & E, 5 x 20).

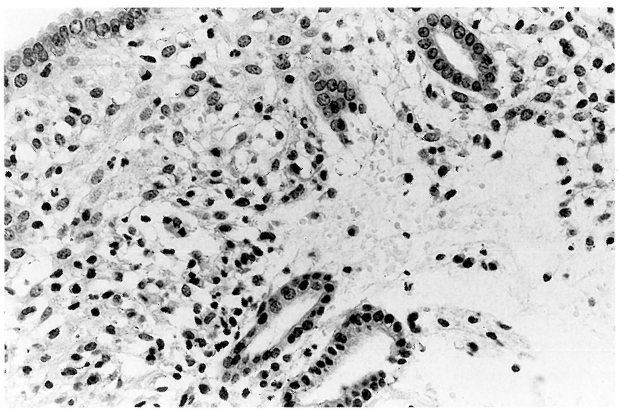

Figure 5. — Case 2. Twenty-nine weeks after treatment with MPA, endometrial glands lined by flattened or cuboid epithelial cells and deciduoid change in stroma. (H & E, 5 x 20).

bed rest and spasmolysis for abdominal distension. The rest of the pregnancy was uncomplicated until 35 weeks of gestation when labor pains started. The patient delivered two normal and healthy infants, with birth weights 2312 g and 2210 g, respectively on September 3, 1998. The placenta seemed to be normal macroscopically.

Following the delivery, the patient was followed-up every four weeks. Endometrial thickness measured by transvaginal ultrasonography was 4 mm and endometrial cytology and biopsy revealed no evidence of recurrent disease 13 months after delivery while she was lactating and amenorrheic. In addition, there was no evidence of distant metastasis.

Case 2

A 34-year-old Japanese woman, nulligravida, had been well until August 31, 1996 when she complained of abnormal vaginal bleeding for eight days. She had a history of regular 28-day menstrual cycles and her basal body temperature recorded for three months revealed regular ovulation. Her last menstrual period had been August 11, 1996 and since then no ovulation was recognized. Dilatation and curettage at a nearby hospital on September 11 revealed endometrial carcinoma and she was referred to Kitasato University Hospital for further examination and treatment on October 31. Pelvic examination revealed no abnormal findings in the uterus and ovaries and her cervix appeared healthy. Her endometrial cytology was positive sug-

gesting adenocarcinoma, while the Pap smear was negative. A fractional curettage showed well-differentiated adenocarcinoma without cervical invasion (Fig. 4). MRI confirmed the absence of myometrial invasion and cervical involvement. With a diagnosis of G1 endometrial carcinoma, clinical stage I, the patient received continuous oral MPA 600 mg/day from November 21, 1996 to July 15, 1997. Atrophic endometrial glands and decidual change in the stroma were evident four weeks after treatment. However, endometrial cytology was positive for malignant cells for the first three months. After 29 weeks of therapy, histology of the endometrium showed atrophic glands with edematous stroma (Fig. 5) and cytology also became negative. Complete regression was confirmed by dilatation and curettage on July 15, 1997. The total dose of MPA was 134,400 mg. Subsequently, 5 courses of cyclic MPA (20 mg/day, P.O.) therapy was given until January 1, 1998. Clomiphen citrate was prescribed for inducting ovulation. The patient had a successful pregnancy with her last menstrual period on May 13, 1998. The course of the pregnancy was uncomplicated and on February 4, 1999 (gestational age: 38 weeks) she delivered a normal infant with a birth weight of 2734 g. Following the delivery, there was no evidence of recurrent disease.

Discussion

Synthetic progestins have been successfully used since the early 1960s in patients with metastatic endometrial carcinoma [10, 11]. Later, Bokhman *et al.* [12] reported that following administration of 500 mg oxyprogesterone caproate daily with a total dose of 10 to 16 g, complete regression of well-differentiated carcinomas was found in 24%, whereas only 6% showed complete regression in moderately or poorly-differentiated lesions. Randall *et al.* [13] reported that in 12 patients under age 40 with well-differentiated adenocarcinoma treated with progestins, nine had regression of their lesions and at a mean follow-up of 40 months, all patients were alive and well without evidence of progressive disease. They concluded that treatment of well-differentiated endometrial adenocarcinoma with progestins appeared to be a safe alternative to hysterectomy in women under age 40. Kim *et al.* also reported that progestin treatment for well-differentiated adenocarcinoma in young women was successful in 13 out of 20 cases [14], although some risk of the progestin treatment was suggested. The risk of disease progression occurring during or after progestin therapy would be approximately 5% [14], while Randall *et al.* [13] did not experience patients with progressive disease except three with persistent lesions, and they reported that the median length of treatment required for regression was nine months. In our cases, the duration of treatment required to achieve regression was 22 weeks and 29 weeks, respectively. It is plausible that patients must be prepared to comply with prolonged treatment with careful and multiple endometrial biopsies.

Christopherson *et al.* advocated that age was one of the most important independent risk factors for stage I endometrial cancer [15]. In their study of 595 patients, 5-year survival in women under age 50 was 100%. In a recent series of 17 women under age 45 with endometrial adenocarcinoma, progestin therapy for two women with pulmonary metastasis developed complete response [16]. In contrast, adjuvant progestin therapy was not found to improve survival in a randomized trial of patients with early endometrial cancer who were not selected for age [17]. These data suggest that endometrial cancer is biologically different in young women. Women under age 40 with well-differentiated adenocarcinoma may be highly responsive to progestin therapy. Therefore, progestin treatment should be considered if these patients desire to preserve their fertility.

Women who succeeded in conceiving following progestin treatment for endometrial cancer have been limited [13, 19-22]. The characteristics of young patients with endometrial carcinoma reported in the literature [2, 3, 18] appeared to be chronic unovulation, obesity, sterility and polycystic ovary, which may be related to prolonged unopposed estrogen stimulation. Both of our patients complained of infertility and case one suffered from chronic unovulation due to polycystic ovary. The high incidence of chronic unovulation and infertility in young women with endometrial carcinoma are considered as the cause of the low pregnancy rate. In our previous experience [23], the carcinoma relapsed soon afterwards, probably because ovulatory function was not controlled appropriately. To permit subsequent pregnancy as well as to prevent the recurrence of carcinoma, it is important to induce ovulation following regression of carcinoma. Therefore, we gave cyclic low dose MPA therapy and then tried to induce ovulation. On the other hand, Kimmig *et al.* [19] reported that progestin treatment should be immediately followed by down-regulatory therapy with GnRH in order to prevent reinduction of the menstrual cycle and unnecessary prolonged exposure to estrogens.

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