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# Endometrioid Endometrial Carcinoma Indirectly Caused by Pituitary Prolactinoma: A Case Report

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## Key Words

Anovulation · Endometrioid adenocarcinoma · Infertility · Menstrual disorder · Prolactinoma

## Abstract

We present the case of a 44-year-old nulliparous woman who experienced irregular menstrual cycles for about 10 years and developed both pituitary prolactinoma and endometrioid endometrial carcinoma. In premenopausal women, hyperprolactinemia causes hypogonadism by inhibiting secretion of gonadotropin-releasing hormone and thus suppressing luteinizing hormone levels, which can cause menstrual disorders ranging from amenorrhea, oligomenorrhea and chronic anovulatory cycle to short luteal phase of the menstrual cycle. A chronic anovulatory menstrual cycle is the most common cause of long-term exposure of the endometrium to endogenous estrogen without adequate opposition from progestins, which can lead to endometrioid endometrial carcinoma. In this case, pituitary prolactinoma may have caused the chronic anovulatory cycle and indirectly led to the endometrioid endometrial carcinoma. In patients for whom the cause of irregular menstruation and chronic anovulatory cycle is suspected to be hyperprolactinemia, explorations of both the hypophysis and endometrium are essential.

## Introduction

Prolactinomas are pituitary adenomas that secrete prolactin. These represent the most common hormone-secreting adenomas occurring in the pituitary gland, accounting for around 40% of all clinically recognized pituitary adenomas [1]. They are

diagnosed more frequently in women than in men, especially between the ages of 20 and 40 years, because premenopausal women are sensitive to hypogonadism, which manifests as infertility and menstrual disorders, whereas postmenopausal women are already hypogonadal and men may ignore or not recognize symptoms of hypogonadism manifesting as decreased libido, impotence, or erectile dysfunction [1]. Moreover, galactorrhea is rare for both postmenopausal women and men (and is also relatively rarer than hypogonadism in premenopausal women), so symptoms due to tumor growth such as headache or visual field loss can represent chances for diagnosis in postmenopausal women or men [2].

Herein, we present the case of a 44-year-old nulliparous woman who had experienced irregular menstruation cycles for about 10 years and developed both pituitary prolactinoma and endometrioid endometrial carcinoma. In premenopausal women, hyperprolactinemia causes hypogonadism by inhibiting the secretion of gonadotropin-releasing hormone, which in turn suppresses luteinizing hormone levels and can cause menstrual disorders ranging from amenorrhea, oligomenorrhea and chronic anovulatory cycle to short luteal phases of the menstrual cycle [3–5]. Chronic anovulatory menstrual cycle is the most common cause of long-term exposure of the endometrium to endogenous estrogen without adequate opposition from progestins, which can lead to endometrioid endometrial carcinoma [6, 7]. Thus, in this case, pituitary prolactinoma may have caused the chronic anovulatory cycle and indirectly led to the development of endometrioid endometrial carcinoma.

## Case Report

A nulliparous 44-year-old woman with a 10-year history of irregular menstrual cycles presented with massive abnormal uterine bleeding, shortness of breath, and exhaustion. She had experienced abnormal uterine bleeding for about 1 year, and it had increased over the previous 10 days. She had no past illnesses of note, including no history of hypertension or glucose intolerance, and no special history of taking pharmacotherapies.

On presentation, she was obese with a height of 152 cm and weighing 73.0 kg. Vital signs were stable, with: blood pressure, 152/96 mm Hg; heart rate, 88 beats/min; axillary temperature, 100.2°F; and oxygen saturation by pulse oximetry, 99% (room air). General physical examination revealed hirsutism without any other signs of androgen excess such as acne, male pattern baldness, or lowering of the voice, and there was no evidence of galactorrhea. Gynecological examination revealed an almost normal-sized uterus, impalpable bilateral adnexa, and unremarkable vagina and vulva. Bleeding from the external cervical os was evident. Ultrasonographic examination and magnetic resonance imaging (MRI) showed thickening of the endometrium and collapse of the junctional zone. Both ovaries appeared normal and no fluid was evident in the pelvic cavity (fig. 1). Endometrial curettage revealed well- to moderately differentiated endometrioid carcinoma (FIGO grade 1). Hemoglobin level was 6.6 g/dl, and blood glucose level was normal.

Surgical resection was planned for the endometrial carcinoma. While waiting for the operation, correction of anemia by iron supplementation and exploration of the reasons for irregular menstruation were initiated. Endocrinological survey yielded the following results: serum prolactin, 243.8 ng/ml (institutional normal range, 4.1–28.6); luteinizing hormone, 2.0 mIU/ml (follicular phase, 1.7–13.3); follicle-stimulating hormone, 7.2 mIU/ml (follicular phase, 4.5–11.0); estradiol, <25.0 pg/ml (follicular phase, 40.7–224.0); testosterone, 23 ng/dl (normal, 9–56); growth hormone, 0.05 ng/ml (normal, 0.28–1.64); adrenocorticotrophic hormone, 16.2 pg/ml (normal, 7.2–63.3); thyroid-stimulating hormone, 2.95  $\mu$ IU/ml (normal, 0.38–4.31). Marked hyperprolactinemia led us to suspect pituitary prolactinoma, and MRI of the hypophysis was therefore performed. T1-weighted MRI showed an 8.4  $\times$  7.8-mm tumor in the right anterior lobe of the hypophysis (fig. 2). No evidence of

headache or visual field loss was present, so surgery did not seem to be indicated for the pituitary prolactinoma.

A few days later, total abdominal hysterectomy was performed with bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy. Histological examination confirmed grade 2, well- to moderately differentiated endometrioid endometrial carcinoma tumors with less than half myometrial invasion and without involvement of any other organs, including regional lymph nodes.

During the 10 months of follow-up, serum prolactin levels have been stable at around 160 ng/ml, and no signs of recurrence of endometrial carcinoma have been present.

## Discussion

The prognosis of advanced-stage endometrial carcinoma is still poor relative to early-stage carcinoma, although many improvements have been made in treatment modalities such as surgery, chemotherapy, radiotherapy and others in recent years. Remembering risk factors for endometrial carcinoma, detecting patients in high-risk groups, and dealing properly with them, are thus important for catching early-stage patients and decreasing the morbidity and mortality rates of this life-threatening disease. In particular, in endometrioid endometrial carcinoma, which comprises about 80% of endometrial carcinomas, long-term exposure to excess estrogen unopposed by progestin is well known as the most important risk factor [7, 8]. Chronic anovulatory menstrual cycle remains the most common cause of long-term, unopposed exposure of the endometrium to endogenous estrogen [6, 7].

Many endocrinological disorders cause ovulatory disorders, with polycystic ovary syndrome (PCOS) as the most representative. Because the patient was obese with hirsutism, the ovulatory disorder was initially attributed to PCOS. However, no high serum androgen levels or polycystic ovaries were identified on imaging. PCOS was therefore ruled out. Rather, hyperprolactinemia and underlying pituitary prolactinoma were identified. Although the causes of hyperprolactinemia vary widely, marked hyperprolactinemia over 200–250 ng/ml is usually due to pituitary prolactinoma or pregnancy [9], and this was also evident in the present patient.

In premenopausal women, hyperprolactinemia causes hypogonadism by inhibiting secretion of gonadotropin-releasing hormone followed by suppression of luteinizing hormone levels and can cause menstrual disorders ranging from amenorrhea, oligomenorrhea and chronic anovulatory cycle to short luteal phases of the menstrual cycle. As mentioned above, chronic anovulatory cycle can be a risk factor for endometrioid endometrial carcinoma, and this patient had a 10-year history of irregular menstruation. Pituitary prolactinoma could thus have indirectly resulted in endometrioid endometrial carcinoma through chronic anovulatory cycle in this case. Indeed, some anecdotal evidence from similar cases suggests a relationship between hyperprolactinemia and endometrioid carcinoma [10–12]. In this case, obesity could also have been a cause of ovulatory disorder, in addition to pituitary prolactinoma. Obesity is thought to have various carcinogenic effects other than ovulatory disorder for endometrial carcinoma [7]. However, cases of endometrial carcinoma correlating with hyperprolactinemia have involved younger patients compared to the more common obese cases without hyperprolactinemia [10, 12]. Pituitary prolactinoma could thus have been more important than obesity as a cause of carcinoma in this case.

One apparent inconsistency is that plasma estrogen concentrations on presentation were subnormal, while estrogen exposure is theoretically needed for carcinogenesis. Actually, we do not have any information about her hormone levels (including prolactin) prior to her presentation to our hospital, after irregular menstruation had been ongoing for a long period. However, some studies have proposed that increased plasma estrogen concentration is not important for carcinogenesis; rather, long-term exposure to low concentrations of estrogen unopposed by progesterone (that is, under conditions of progesterone deficiency) plays an essential role [6, 7, 11].

Another area of uncertainty involves the direct effect of prolactin on the endometrium, rather than the indirect effect mentioned above. Although some studies have reported that serum concentrations of prolactin are significantly elevated in patients with endometrial carcinoma compared to healthy individuals [13, 14] and that prolactin receptors are expressed in both normal endometrial and carcinoma tissue [14, 15], the direct effects of prolactin on the endometrium, in terms of proliferative or differentiative effects, remain unclear. The utility of correcting hyperprolactinemia using dopamine agonists for the purpose of preventing the development of endometrial carcinoma has yet to be determined. In the present case, levels of serum prolactin have remained stable and no evidence of recurrent endometrial carcinoma has been identified during follow-up.

In conclusion, hyperprolactinemia indirectly induces endometrioid endometrial carcinoma after causing chronic anovulation. In patients with irregular menstruation and chronic anovulation that may be attributable to hyperprolactinemia, exploration of both the hypophysis and endometrium is essential.

### Acknowledgements

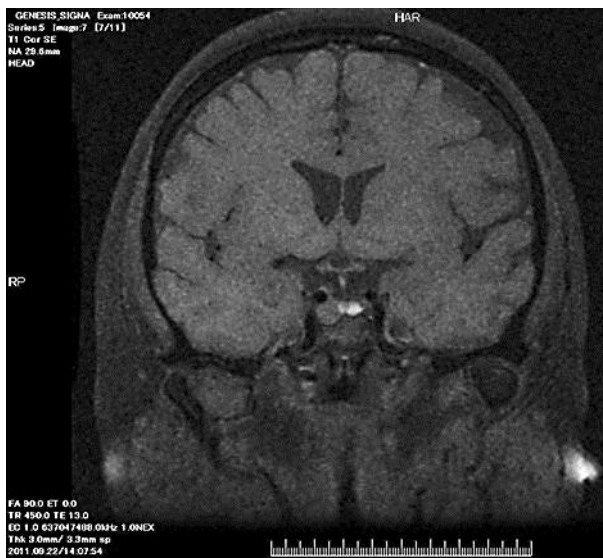
No funding was received for this study.

### Disclosure

None of the authors have any conflicts of interest to declare.



**Fig. 1.** T2-weighted MRI of the uterus, showing a thickened endometrium and collapse of the junctional zone.



**Fig. 2.** T1-weighted MRI of the hypophysis, showing an 8.4 × 7.8-mm tumor in the right anterior lobe.

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