NOTE

A case of functioning gonadotroph adenoma in a reproductive aged woman

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Abstract. A 34-year-old woman presented our hospital with complaint of irregular menstruation and abnormal uterine bleeding lasting for a month. After her second parturition at the age of 27, her menstrual cycle had been regular, but it suddenly became irregular at the age of 30. Transvaginal ultrasound revealed the presence of ovarian mass, and the patient underwent diagnostic laparoscopic surgery. Bilateral ovaries temporally shrink after puncture but the size soon resumed. Gonadotropins were almost normal, but estradiol and PRL levels turned out to be elevated, and cabergoline treatment was initiated. After referral to our hospital, we found that the ovaries showed multifollicular appearance. Brain magnetic resonance imaging showed an 18-mm macroadenoma in the suprasellar area. To suppress the secretion of endogenous gonadotropins and estrogen, low-dose estrogen-progestin was prescribed. Surprisingly, the treatment temporarily reduced the size of the ovaries. The patient was referred to a neurosurgeon, and a functioning gonadotroph adenoma was suspected. After the resection of the pituitary tumor, her menstrual cycle became regular, and the size of bilateral ovaries became normal. We also noticed that her ovarian reserve judged by anti-Müllerian hormone had been almost diminished after the surgical treatment, probably reflecting the exhaustion of follicular pool. Women with multifollicular ovaries and elevated estradiol levels may have functioning gonadotroph adenomas, although the level of FSH is relatively normal, and ovarian reserve can be followed by measuring anti-Müllerian hormone.

Key words: Functioning gonadotroph adenoma, Multifollicular ovaries, Reproductive aged woman, Hyperprolactinemia

THE CASE of functioning gonadotroph adenomas that produce FSH was first described in 1974 [1]. The disease is usually recognized in middle-aged men who have visual impairment, such as decreased vision, seizures, and headaches resulting from enlarged adenomas [2], and the common clinical characteristics are the hypersecretion of FSH. The diagnosis of functioning gonadotroph adenoma in postmenopausal women can be extremely difficult because women after final menstrual period exhibit elevated serum FSH level and the secretion of FSH by adenomas is indistinguishable. A few cases of functioning gonadotroph adenomas in reproductive aged women have been reported and clinical manifestations of the patients are irregular menstrual cycles or amenorrhea, often with enlarged ovaries [3]. The diagnosis FSH-producing pituitary adenomas in reproductive aged

women can also be difficult because FSH level could fluctuate during menstrual cycle, and women in their 30s exhibit various levels of estrogen considering that the level of FSH reflects ovarian reserve. Here, we report a case of a reproductive aged woman with normal FSH serum levels who exhibited enlarged multifollicular ovaries.

Case Report

A 34-year-old woman was referred to our hospital because of her irregular menstrual cycles and abnormal uterine bleeding lasting for a month. Her past clinical history and family history before her parturitions were unremarkable. Three years after her second parturition, her menstrual cycle became irregular. Her menstrual cycle became normal after receiving oral contraceptive pills, but she quit taking oral contraceptive pills due to heavy nausea and vomit attributed to the side effects of oral contraceptive pills. The previous doctor found enlarged multifollicular ovarian tumor by transvaginal ultrasound. Laboratory data were obtained including

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Fig. 1 Transvaginal ultrasound examination showed multifollicular bilateral ovaries.

A. The right ovary was 7 cm in diameter and polycystic.

B. The left ovary was 5 cm in diameter.

GnRH test and the data indicated elevated estradiol and PRL levels [FSH (mIU/mL); 7.88 (0 min), 8.13 (30 min), LH (mIU/mL); 0.3 (0 min), 1.61 (30 min), PRL (ng/mL); 71.51 (0 min), 31.68 (60 min)]. To exclude the possibility of ovarian cancer, the patient underwent diagnostic laparoscopic surgery. Puncture during operation procedure had an influence to reduce the volume of the ovaries, however, the ovaries became enlarged again soon after the operation, and abnormal uterine bleeding started. Although she had no symptom of galactorrhea, cabergoline treatment was initiated to suppress the secretion of PRL. However, her menstrual cycle remained irregular and abnormal uterine bleeding continued. As a result, the patient was referred to our hospital. The laboratory data upon visit of our facility showed that the serum FSH was 12.3 mIU/mL, LH was 0.2 mIU/mL, PRL 4 ng/mL, estradiol (E_2) was 180.4 pg/mL, progesterone (P_4) was 2.4 ng/mL, and AMH (anti-Müllerian hormone) was 1.01 ng/mL. A transvaginal ultrasound examination revealed a myoma in the uterus, and bilateral ovaries were enlarged, resembling the ovaries under controlled ovarian stimulation in *in vitro* fertilization program (Fig. 1). Magnetic resonance imaging (MRI) revealed the presence of a pituitary tumor in the suprasellar area (Fig. 2), thus we suspected the possibility of pituitary prolactinoma. Considering that the FSH level was slightly increased and E_2 level was also increased, we prescribed low-dose estrogen-progestin (LEP) that contains drospirenone 3 mg and ethinylestradiol 0.02 mg/day. Cyclic regimen for 16 weeks was continued and LEP temporarily suppressed the pituitary-gonadotropin axis, and ovarian volume decreased; however, the ovarian swelling soon resumed. The patient was referred to a neurosurgeon. In the 500 ng thyrotropin-releasing hormone (TRH) test, serum PRL levels increased from 14 to 44.6 ng/mL, and TSH levels increased from 0.107 to 1.191 mIU/mL at 30 min after administration. In the 100 ng gonadotropin-releasing hormone (GnRH) test, serum

FSH was increased from 5.9 to 9.7 mIU/mL, the LH level was increased from 1.8 to 11.5 mIU/mL at 30 min after administration, and the serum FSH level was increased continuously. Taken together, a functioning gonadotroph adenoma was suspected, and the patient underwent resection of the pituitary tumor. Immunohistochemical examination of the resected adenoma showed intense reactivity for FSH and LH (Fig. 3). Finally, her menstrual cycle became regular, and the ovaries became normal in size and AMH was 0.61 ng/mL after the surgery. Six months later, AMH was below detection level (less than 0.1 ng/mL). A functioning gonadotroph adenoma recurred at four years later, so the patient underwent Gamma Knife radiosurgery. At the time of recurrence, her ovaries were normal. She had no symptoms after the surgery and her menstruation remained to be normal.

Discussion

Functioning gonadotroph adenoma was initially considered to be rare, but recent studies have shown that these tumors account for 20 to 25% of all pituitary macroadenomas in men [2, 4]. Histological evidence shows that functioning gonadotroph adenomas occur as frequently in women as they do in men [5, 6]. The clinical features of functioning gonadotroph adenomas might differ between men and women because the ovaries exhibit multifollicular appearance due to the continuous stimulation by FSH in reproductive aged women, and it can be difficult to diagnose functioning gonadotroph adenomas in postmenopausal women who already have elevated serum concentrations of gonadotropins [7]. Approximately 30 cases functioning gonadotroph adenomas in reproductive-aged women have been reported so far [3, 8]. In most of the reported cases, serum FSH levels ranged from normal to high [9], serum LH levels were decreased, E_2 levels ranged from normal to high, and

Fig. 2 Brain MRI showed a 1.8 cm pituitary tumor in the suprasellar area. Arrow head denotes the tumor.

A. Coronal view

B. Sagittal view

Fig. 3 Pathological findings of the tumor. Immunohistochemistry of the tumor showed positive results for FSH and LH and negative results for PRL, TSH, and ACTH (data not shown).

A. In hematoxylin-eosin staining showed spindle-shaped eosinophilic cells.

B. Over 70% of the cells were positive for FSH.

C. Approximately, 10–20% of the cells were positive for LH (magnified by 40 diameters).

serum PRL levels were elevated. The elevated level of FSH from adenomas leads to the formation of multiple ovarian follicles and increasing E_2 levels, which results in decreased LH levels and normal FSH levels by an estrogen-induced negative feedback mechanism [10–12]; however, this mechanism is not present with normal FSH and normal E_2 levels. A case report showed that the serum FSH bioactivity/immunoactivity ratio of a patient with functioning gonadotroph adenoma was mostly equal to that of two healthy subjects by a granulosa cell aromatase assay, suggesting that other explanations may be necessary for multiple ovarian cysts [13]. An abnormal form of FSH from an adenoma may inhibit pituitary LH-releasing hormone (LHRH) receptors or LHRH secretion from the hypothalamus and lead to decreased LH levels [14]. In perimenopause to postmenopausal women, FSH is elevated due to the decrease of E_2 , thus the ovaries of postmenopausal women with functioning gonadotroph

adenomas are often normal in size [8]. In this case, we measured a representative ovarian reserve marker AMH known to be a representative marker for evaluating ovarian reserve, and the changes of AMH during the clinical course of functioning gonadotroph adenoma has not been reported in previous report. This case exhibited decreased AMH level after sphenoidal surgery and the decrement might be attributed to the exhaustion of antral follicles provoked by elevated FSH. We would like to emphasize that this case did not show enlarged ovaries after recurrence of pituitary tumor, and the reason might be hypothesized to the decreased AMH value. Therefore, AMH can be a good marker for predicting ovarian appearance in cases of reproductive aged women.

The treatment for functioning gonadotroph adenomas is transsphenoidal tumor resection. If a tumor is a microadenoma, then medical treatment is effective in some cases [15, 16].

The present case showed normal FSH levels, almost normal estradiol levels, and elevated PRL with enlarged ovaries. Notably, women with multicystic enlarged ovaries and elevated estradiol and prolactin levels may have functioning gonadotroph adenoma, but the ovaries will not be enlarged in patients with decreased ovarian reserve.

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Disclosure

None of the authors have any potential conflicts of interest to disclose.

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