Secondary Amenorrhea with Low Serum Luteinizing Hormone and Follicle-stimulating Hormone Caused by an Inhibin A- and Inhibin B-producing Granulosa Cell Tumor

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SUMMARY

Objective: Here, we report a case of secondary amenorrhea with low serum luteinizing hormone and follicle-stimulating hormone levels due to an inhibin A- and inhibin B-producing granulosa cell tumor of the ovary.

Case Report: A woman aged 26 with infertility, secondary amenorrhea and low levels of gonadotropin was referred to us as a case of hypothalamic amenorrhea. There was a mass measuring 56 × 41 mm in her right adnexa. We were suspicious of malignancy and checked the tumor marker levels. Laboratory findings showed high levels of inhibin A and B. She underwent an exploratory laparotomy. Microscopic examination revealed an adult granulosa cell tumor. Eighteen days after excision, she had spontaneous menstruation with normal levels of follicle-stimulating hormone and luteinizing hormone.

Conclusion: A granulosa cell tumor secretes inhibin A and B, which suppress follicle-stimulating hormone and luteinizing hormone release through a central mechanism. This leads to amenorrhea, which can be misdiagnosed as hypothalamic amenorrhea. Inhibin-producing ovarian tumors must be considered in the assessment of patients with apparent hypothalamic amenorrhea. [*Taiwan J Obstet Gynecol* 2009;48(1):72–75]

Key Words: follicle-stimulating hormone, granulosa cell tumor, inhibin A, inhibin B, luteinizing hormone

Introduction

Pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) is regulated by feedback of ovarian hormones. Estradiol enhances LH and inhibits FSH secretion; inhibin A and inhibin B decrease FSH synthesis and release [1]. Inhibins are heterodimeric glycoproteins, belonging to the transforming factor-B growth family and are produced by granulosa cells of the ovarian follicles [2]. Inhibin A and inhibin B have an equipotent capacity to inhibit FSH secretion from pituitary cells [3]. Ovarian granulosa cell tumors (GCTs) arise from the sex cord stromal cells of the ovary and account for 2–3% of all ovarian cancers [4]. GCTs have two distinct subtypes, the adult and the juvenile type, based on histopathologic and clinical features [2]. Lappohn et al reported that patients with a GCT have high serum inhibin levels, so the GCT produces inhibin [5]. Other studies have confirmed that inhibin B almost always increases in patients with a GCT [6]. Initially, immunoassays of inhibins could not distinguish between inhibin A and B. With the development of specific immunoassays, these forms can be recognized separately [7]. In patients with a GCT, serum inhibin A and B concentrations were elevated by 67% and 89%, respectively [2]. Hypothalamic amenorrhea is characterized by amenorrhea, low or low-normal levels of FSH, LH and estradiol, and normal levels of prolactin [1]. In the reproductive years, low levels of FSH, caused by an inhibin-producing GCT, can lead to amenorrhea through a central mechanism. Moreover, it can be misdiagnosed

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as hypothalamic amenorrhea. We report the case of a woman with an inhibin A- and inhibin B-producing GCT who presented with secondary amenorrhea, low levels of FSH and LH, and normal prolactin level that resembled hypothalamic amenorrhea.

Case Report

A woman aged 26 was referred to the infertility clinic of Doctor Shariati Hospital with 3 years' primary infertility since her marriage. She had a history of secondary amenorrhea over the previous 4 years. Withdrawal bleeding was induced with medroxyprogesterone acetate. Progression of puberty was normal. Menarche had occurred at 13 years, with regular menses until 4 years previously. Her weight and height were 65 kg and 160 cm, respectively. There was no evidence of hirsutism. Laboratory studies showed FSH 0.1 U/L, LH 1.4 U/L, estradiol 100 pg/mL, testosterone 0.4 ng/mL (normal range, 0.1–1.0 ng/mL), free testosterone 2.3 pg/mL (normal range, 0.04–4.4 pg/mL), prolactin 16.9 ng/mL (normal range, 3.0–33 ng/mL), thyroid stimulating hormone 2.2 mIU/L (normal range, 0.2–4.9 mIU/L), dehydroepiandrosterone sulfate 2.1 μg/mL (normal range, 0.4–3.1 μg/mL). She was referred as a case of hypothalamic amenorrhea, with low levels of FSH and LH, normal prolactin level and secondary amenorrhea. On pelvic examination, we found a mobile, non-tender, well-defined mass. Abdominal ultrasonography in the early follicular phase revealed a heterogeneous solid cystic mass in the right adnexa measuring 56 × 41 mm, and the endometrial thickness was 6 mm. Color-flow Doppler imaging of the ovary revealed a low-resistance vessel that is consistent with neovascularization in malignancy (resistance index, 0.45; pulsatility index, 0.75). We suspected malignancy and checked tumor markers that were: α-fetoprotein 1.7 U/mL (normal range, ≤ 7 U/mL), carcinoembryonic antigen 0.6 ng/mL (normal range, < 4 ng/mL), β-human chorionic gonadotropin 0 IU/L, CA-125 20.5 U/mL (normal range, < 35 U/mL), lactate dehydrogenase 311 U/L (normal range, 225–500 U/L), inhibin A 255 ng/mL (normal range, 4–150 ng/mL), inhibin B 1,124 ng/mL (normal range, 15–200 ng/mL). Inhibin A and B were measured using specific two-site enzyme immunoassays (Serotec, Oxford, UK). The patient underwent an exploratory laparotomy. There was a mobile encapsulated right ovarian mass, measuring 6 × 5 cm. The left tube and ovary were normal, there was no sign of spread to other pelvic organs and there was no significant ascites. A frozen section of resected tumor indicated a GCT, so we performed a right salpingo-oophorectomy,

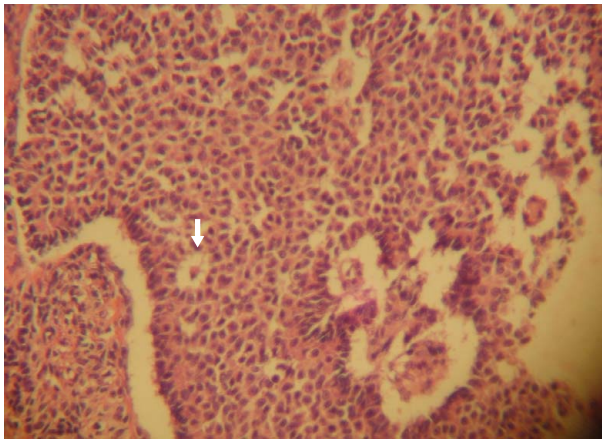

Figure 1. Microscopic features of the granulosa cell tumor show neoplastic cells with Call-Exner bodies (arrow) (hematoxylin and eosin, 100×).

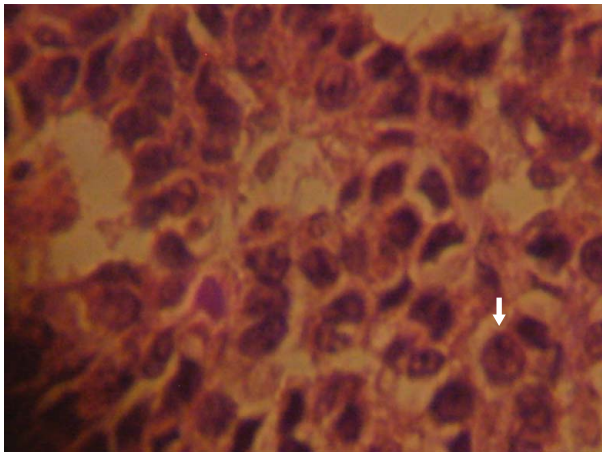

Figure 2. Microscopic features of the granulosa cell tumor show nuclear grooves (coffee-bean appearance) of the neoplastic cells (arrow) (hematoxylin and eosin, 400×).

peritoneal washing, partial omentectomy, and pelvic and para-aortic lymph node sampling. Pathologic examination confirmed an adult GCT confined to the right ovary with no lymphovascular invasion. The fallopian tube, omentum, peritoneum and lymph nodes were free from the tumor (stage Ia). The neoplastic cells showed a classic adult GCT with coffee-bean appearance of tumor cell nuclei. There were both well and moderately differentiated areas, replete with microfollicular and macrofollicular patterns with many Call-Exner bodies. No poorly differentiated area, unusual mitotic figures or necrosis was observed (Figures 1 and 2). Eighteen days after surgery, she had spontaneous menstruation. An LH surge-detecting kit confirmed ovulation. At day 3 of the first menstruation, the serum levels of FSH, LH and estradiol were 6.4 U/L, 5.3 U/L and 46 pg/mL, respectively. Postoperative levels of inhibin B and inhibin A were 105 ng/mL and 64 ng/mL, respectively.

Discussion

Hypothalamic amenorrhea is characterized by amenorrhea, low or low-normal levels of FSH, LH and estradiol, and a normal level of prolactin. This diagnosis represents one of the most common forms of anovulation and can be defined only after exclusion of pituitary and ovarian abnormalities [1]. Functional hypothalamic amenorrhea is often due to psychogenic stress, weight changes, undernutrition, and excessive exercise. Infrequently, hypothalamic dysfunction occurs before menarche and presents as primary amenorrhea [8]. A GCT secretes inhibin A and B, which inhibit FSH release from the pituitary leading to amenorrhea with low levels of FSH. Thus in premenopausal women, who present with hypothalamic amenorrhea, it is necessary to rule out the possibility of an ovarian tumor. Lappohn et al [5] reported three women with secondary amenorrhea and infertility due to a GCT; in one case, both FSH and LH levels were low, and in two cases, only FSH levels were below the normal range. To the best of our knowledge, this is the only case report that has been presented so far which had a hormonal profile similar to our patient. In our case, both FSH and LH levels were low. Despite the low levels of FSH and LH, estradiol levels were in the normal range, because the majority of GCTs produce estrogen. After surgery, as a consequence of removing the tumor, estradiol levels decreased. By definition, inhibin suppresses only basal FSH secretion from the pituitary. However, an *in vitro* study suggested that at higher concentrations, inhibin partially suppresses basal LH release [9,10].

Kurihara et al [11] reported a patient aged 31 years with an inhibin B-secreting GCT who presented with secondary amenorrhea. She had normal levels of LH and estradiol and low levels of FSH. After removal of the tumor, the serum levels of FSH and inhibin B returned to normal. They concluded that in premenopausal women, secondary amenorrhea may be the initial manifestation of a GCT [11]. In a patient with a GCT, the most common presenting symptom at menopause is postmenopausal bleeding due to prolonged exposure to tumor-derived estrogen. In contrast, premenopausal women may develop irregular menses or, less often, secondary amenorrhea [12]. Moreover, the most common sign of the tumor in women with a uterus is oligoamenorrhea that should be considered by clinicians [4]. Krishnan et al [13] reported a woman aged 36 years presenting with infertility, secondary amenorrhea, and low levels of FSH similar to isolated FSH deficiency. They termed it a pseudo-isolated FSH deficiency due to an inhibin B-secreting GCT leading to low levels of FSH with normal estradiol levels [13]. Not only does the GCT have the capacity to produce high levels of inhibin A and B, but other ovarian tumors, such as mucinous cyst adenocarcinoma and fibrothecoma, also release inhibin. It was shown that in patients with mucinous cyst adenocarcinoma, inhibin B and inhibin A increased by 60% and 20%, respectively [14]. In patients with ovarian fibrothecoma, inhibin A and B increased by 71% [15].

Not all patients with GCTs have elevated levels of inhibin A and B. It was shown that inhibin B increased in 89% and inhibin A in 67% of patients with GCTs (60-fold and sevenfold the normal ranges, respectively) [2]. Therefore, inhibin B markedly increases in patients with GCTs. Inhibin A, meanwhile, increases only slightly. In our case, both inhibin A and inhibin B increased to 255 ng/mL and 1,124 ng/mL, respectively. Our patient had normal puberty, regular menstruation preceding amenorrhea, and normal body mass index. Initially, she was diagnosed as a case of hypothalamic amenorrhea. Ovarian tumors such as a GCT, fibrothecoma and mucinous cystadenocarcinoma secrete inhibin. This results in low levels of FSH and LH with secondary amenorrhea similar to hypothalamic amenorrhea. It appears that in the assessment of a patient initially diagnosed with hypothalamic amenorrhea, it is necessary to rule out an inhibin-producing ovarian tumor. This warrants evaluation of both ovaries with sonography and measurement of serum inhibin A and B. In addition, the presence of low FSH levels coupled with normal levels of estradiol in a patient with amenorrhea warrants further evaluation of inhibin A and B. Elevated levels of inhibins in these patients must alert us to the possible presence of inhibin-producing ovarian tumors.

References

1. Marshall JC, Eagleson CA, McCartney CR. Hypothalamic dysfunction. *Mol Cell Endocrinol* 2001;183:29–32.
2. Mom CH, Engelen MJ, Willemse PH, Gietema JA, ten Hoor KA, de Vries EG, van der Zee AG. Granulosa cell tumors of the ovary: the clinical value of serum inhibin A and B levels in a large single center cohort. *Gynecol Oncol* 2007;105:365–72.
3. Petraglia F, Hartmann B, Luisi S, et al. Low levels of serum inhibin A and inhibin B in women with hypergonadotropic amenorrhea and evidence of high levels of activin A in women with hypothalamic amenorrhea. *Fertil Steril* 1998;70:907–12.
4. Unkila-Kallio L, Tiitinen A, Wahlström T, Lehtovirta P, Leminen A. Reproductive features in women developing ovarian granulosa cell tumour at a fertile age. *Hum Reprod* 2000;15:589–93.
5. Lappohn RE, Burger HG, Bouma J, Bangah M, Krans M, de Bruijn HW. Inhibin as a marker for granulosa-cell tumors. *N Engl J Med* 1989;321:790–3.

6. Petraglia F, Luisi S, Pautier P, Sabourin JC, Rey R, Lhomme C, Bidart JM. Inhibin B is the major form of inhibin/activin family secreted by granulosa cell tumors. *J Clin Endocrinol Metab* 1998;83:1029–32.
7. Groome NP, Illingworth PJ, O'Brien M, Pai R, Rodger FE, Mather JP, McNeilly AS. Measurement of dimeric inhibin B throughout the human menstrual cycle. *J Clin Endocrinol Metab* 1996;81:1401–5.
8. Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2006;86(Suppl):S148–55.
9. Farnworth PG, Robertson DM, de Kretser DM, Burger HG. Effects of 31 kDa bovine inhibin on FSH and LH in rat pituitary cells in vitro: antagonism of gonadotrophin-releasing hormone agonists. *J Endocrinol* 1988;119:233–41.
10. Messinis IE. Ovarian feedback, mechanism of action and possible clinical implications. *Hum Reprod Update* 2006;12: 557–71.
11. Kurihara S, Hirakawa T, Amada S, Ariyoshi K, Nakano H. Inhibin-producing ovarian granulosa cell tumor as a cause of secondary amenorrhea: case report and review of the literature. *J Obstet Gynaecol Res* 2004;30:439–43.
12. Crew KD, Cohen MH, Smith DH, Tiersten AD, Feirt NM, Hershman DL. Long natural history of recurrent granulosa cell tumor of the ovary 23 years after initial diagnosis: a case report and review of the literature. *Gynecol Oncol* 2005;96: 235–40.
13. Krishnan A, Murdock C, Allard J, Cisar M, Reid E, Nieman L, Segars J. Pseudo-isolated FSH deficiency caused by an inhibin B-secreting granulosa cell tumour: case report. *Hum Reprod* 2003;18:502–5.
14. Burger HG, Fuller PJ, Chu S, et al. The inhibins and ovarian cancer. *Mol Cell Endocrinol* 2001;180:145–8.
15. Hildebrandt RH, Rouse RV, Longacre TA. Value of inhibin in the identification of granulosa cell tumors of the ovary. *Hum Pathol* 1997;28:1387–95.