Clinical Case Seminar

Successful Pregnancy after Bromocriptine Therapy in an Anovulatory Woman Complicated with Ovarian Hyperstimulation Caused by Follicle-Stimulating Hormone-Producing Plurihormonal Pituitary Microadenoma

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Gonadotropin-producing pituitary adenomas are extremely rare in reproductive-age women. We report here a case of gonadotroph microadenoma with ovarian hyperstimulation. It was found in a 29-yr-old infertile Japanese woman with enlarged multicystic ovaries. The patient had an elevated basal serum estradiol level (up to 6755 pM, or 1840 pg/ml). Serum FSH and prolactin were mildly elevated (15.4 IU/liter, 1.4 nM or 31.4 ng/ml), whereas LH was low (0.5 IU/liter). The FSH level was paradoxically elevated in response to TRH administration. Dynamic magnetic resonance imaging revealed a pituitary microadenoma. Daily administration of bromocriptine, a dopamine agonist, normalized the ovarian size, and the patient ovulated naturally. She conceived after 3 months of bromocriptine therapy and delivered a normal child. She underwent elective transsphenoidal pituitary surgery, 3 yr after the delivery. Immunostaining of the resected tumor showed that 80% and less than 5% of the tumor cells stained for FSH-β and prolactin, respectively. Furthermore, RT-PCR suggested that dopamine type 2 receptor was expressed in the adenoma. Gonadotroph microadenoma should be considered in women with spontaneous ovarian hyperstimulation, even if they have no neurological symptoms or marked pituitary enlargement. In such cases, bromocriptine therapy may be an alternative to pituitary surgery. (J Clin Endocrinol Metab 88: 1988–1993, 2003)

Spontaneous Ovarian Hyperstimulation is extremely rare, although exogenous gonadotropin stimulation may frequently cause ovarian hyperstimulation syndrome. In addition to a few pregnant women who have hypothyroidism or polycystic ovary syndrome or factor V Leiden mutation (1–3), only a limited number of cases of spontaneous ovarian hyperstimulation attributable to the gonadotroph adenoma have been reported to date (4–10). Transsphenoidal tumor resection was performed in all of these macroadenoma cases. Some nonsurgical treatments for gonadotroph adenoma are also known, including GnRH analogs and dopamine agonist, although their effects have not been fully determined. We report here the first case of an infertile woman with a gonadotroph microadenoma causing ovarian hyperstimulation. This is also the first case of pregnancy and delivery after successful bromocriptine treatment of such a patient.

Subject and Methods

Serum LH and FSH levels were measured by immunoradiometric assays using Spac-S LH and FSH kits from Daiichi Pharmaceutical Company Ltd. Radioisotope Laboratory (Tokyo, Japan). The detection limit in both of these assays was 0.5 IU/liter. No cross-reactivity with TSH, human CG, FSH, or LH was detectable. Glycoprotein hormone α-subunit was measured by a two-site chemiluminescent immunoassay. Estradiol, progesterone, and testosterone levels were determined by RIA using a kit from Diagnostic Products (DPC; Los Angeles, CA). The detection limit of the DPC estradiol kit was 29.4 pm (8 pg/ml; measurement range, 29.4–13,950 pm). The inters assay variation was less than 7% coefficient of variation. The cross-reactivity with estrone and estriol was 1.03% and 0.32%, respectively. The detection limit of the DPC progesterone kit was 0.06 nm (0.02 ng/ml; measurement range, 0.06–127 nm). The measurement range of the DPC testosterone kit was 0.14–55.5 nm (4–1,600 ng/dl). The cross-reactivity with cortisol and estradiol was 0.005% and 0.02%, respectively. Prolactin (PRL) was measured by RIA using PRL Ribead II from Dainabot (Tokyo, Japan). The measurement range was 0.01–9.10 nm (0.3–200 ng/ml). No cross-reactivity was detectable at concentrations under 3,000 IU/liter for LH, 1,000 IU/liter for FSH, and 1 IU/liter for TSH. GH was measured by immunoradiometric assay using a kit from Daiichi Radioisotope Laboratory. An enzyme immunoassay was used for the determination of serum TSH values, with an AIA-PACK TSH kit (TOSOH Medics, San Francisco, CA). The cross-reactivity with LH was 0.17%; and that with human CG, FSH, and human GH was less than 0.01%. The TRH test was performed to evaluate the response of the anterior pituitary gland. Five hundred micrograms of TRH were administered iv, and serum FSH and LH levels were measured at 0, 15, 30, 60, 90, and 120 min.

Magnetic resonance imaging (MRI) was performed with a Vizard System (1.5-tesla MRI imaging system; Toshiba Medical Systems, Tokyo, Japan).
A 29-yr-old nulligravid Japanese woman consulted the Department of Obstetrics and Gynecology, Anjo Kosei Hospital, with complaint of infertility. She was 150 cm tall and weighed 40 kg. She had irregular menstrual periods, and her basal body temperature record indicated anovulatory cycles. X-Ray CT (Fig. 1A) and transvaginal ultrasound (Fig. 1B) revealed multicystic megaovaries measuring 110 × 100 × 65 mm (right) and 50 × 62 × 72 mm (left). Ascites was not found in these examinations. Routine blood analysis did not show evidence of elevated hemococoncentration.

The first evaluation of her endocrinologic profile showed the following: serum estradiol, 6,755 pm or 1,840 pg/ml (reference range, 40–84 pm in follicular phase); serum FSH, 15.4 IU/liter (reference range, 5.2–14.4 IU/liter in follicular phase); serum LH, 0.5 IU/liter (reference range, 2.2–7.6 IU/liter in follicular phase); free α-subunit, 1.20 ng/ml (reference range, 0.04–0.38 ng/ml in premenopausal women); serum PRL, 1.4 nm (31.4 ng/ml; reference range <1.4 nm); serum TSH, 1.65 mIU/liter (reference range, 0.75–5.43 mIU/liter); serum ACTH, 2.2 pm or 10 pg/ml (reference range, 1.3–8.0 pm); serum GH, 0.24 nm or 5.21 ng/ml (reference range, 0.01–0.40 nm); serum progesterone, 20.7 nm or 65.9 ng/ml (reference range, 0.6–100.5 nm at luteal phase); and serum testosterone, 0.35 nm or 10.2 ng/dl (reference range, 0.35–2.08 nm).

Serum FSH was inappropriately high, considering the high serum estradiol levels, and both serum FSH and LH rose rapidly after TRH administration.

| TABLE 1. Serum hormone concentrations in response to administration of 500 μg TRH |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | FSH (IU/liter) | LH (IU/liter)  |
| Preoperation Postoperation       | Preoperation    | Postoperation   |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| 0 min                           | 17.0            | 9.4             | <0.5            | <0.5            |
| 15 min                          | 23.9            | 12.1            | 0.8             | <0.5            |
| 30 min                          | 26.2            | 12.7            | 0.8             | <0.5            |
| 60 min                          | 24.8            | 12.8            | 0.8             | <0.5            |
| 90 min                          | 23.4            | 11.7            | <0.5            | <0.5            |
| 120 min                         | 22.4            | 10.5            | <0.5            | <0.5            |
levels were elevated in response to TRH (Table 1). We suspected gonadotropinoma and performed a pituitary imaging study to examine this possibility, although the patient did not have visual disturbance or other neurological signs; confrontation screening of visual fields by finger counting was normal. The imaging study revealed a microadenoma in the anterior pituitary lobe.

GnRH agonist (busereline acetate Suprecur, 900 μg daily; Aventis Pharma Japan, Tokyo, Japan) was first administered to the patient for 3 months. However both her FSH and estradiol levels were elevated (FSH, 15.4 to 35.7 IU/liter; estradiol, 6,755 to 13,546 pm or 1,840 to 3,690 pg/ml) and continued to be high despite the treatment. Furthermore, progesterone was also positive (8.2 nm or 0.5 ng/ml). Based on these unfavorable results, we initiated bromocriptine therapy (Parlodel, 5 mg daily; Novartis Pharmaceuticals, Tokyo, Japan), expecting tumor shrinkage. After bromocriptine treatment for 4 wk, the patient’s FSH and estradiol levels gradually decreased to within the normal range (FSH, 8.9 IU/liter; estradiol, 507 pm or 138 pg/ml; progesterone, 1.6 nm or 0.5 ng/ml); and also, transvaginal ultrasound revealed a marked decrease of ovarian size (Fig. 1C).

The patient also began to have regular menstrual periods again and successfully became pregnant. Her course of pregnancy was uneventful, but both ovaries gradually became enlarged in spite of the continued bromocriptine treatment until the 34th week of gestation. Her estradiol level was high (up to 58,000 pm or 15,800 pg/ml), but her serum FSH level remained in the normal range (5.1–8.4 IU/liter). She delivered a healthy male baby weighing 2,980 g.

In the postpartum period, the patient’s serum FSH level became reelevated, and both ovaries became enlarged and multicystic, as when she first visited. Therefore, she again started to take bromocriptine. She ovulated a few times during this period but failed to get pregnant. During the next 3 yr, in spite of an increased dosage of bromocriptine (up to 10 mg), her ovaries did not decrease in size, and her serum FSH and estradiol levels did not decrease (FSH, 15.7 IU/liter;
Although she had no neurological symptoms that indicated macroadenoma in the pituitary gland and no change in pituitary size in MRI studies, transsphenoidal pituitary surgery was performed after preoperative evaluation of the tumor by 3D-CT, because she strongly desired to conceive another child as soon as possible. The tumor was successfully removed and the postoperative course was uneventful, except for transient diabetes insipidus.

Three months after the surgery, the serum FSH level decreased to within the normal range (from 15.7 to 7.8 IU/liter) and the paradoxical elevation of FSH was not observed (Table 1). Both ovaries were reduced in size, and the patient’s ovulatory cycle recovered 6 months after the operation, although her menstrual cycle was not regular.

**Results**

**Endocrinological evaluation of pituitary adenoma**

The serum estradiol level was constantly high (up to 6,755 pm, or 1,840 pg/ml). The serum FSH was mildly elevated (15.4 IU/liter), but LH was low (0.5 IU/liter). Furthermore, FSH and LH were paradoxically elevated after TRH administration (Table 1).

**Imaging evaluation of pituitary adenoma**

MRI revealed that the pituitary fossa was within the normal size range (Fig. 2A). Microadenoma tissue was demonstrated in the right side of the pituitary by dynamic MRI (Fig. 2B). The location of the tumor was imaged in detail by 3D-processing from the helical x-ray CT images (Fig. 2, C–F). The tumor was 7 mm in diameter and was located in the right anterior lower part of the pituitary fossa.

**Pathological evaluation of pituitary adenoma**

Histologic examination revealed tumor cells with round nuclei and clear cytoplasm. The cells had proliferated in trabecular or nest-like patterns, as is typical for pituitary adenomas (Fig. 3A). Immunohistochemical analysis showed positive reactivity for FSH in the cytoplasm of the majority
of the adenoma cells (Fig. 3B). Some of the tumor cells were positive for PRL (Fig. 3C). However, no reactivity for TSH, GH, ACTH, LH, or D2R was detected (data not shown).

**D2R mRNA expression in gonadotroph pituitary adenoma**

The presence of FSH-β, LH-β, and α-subunit mRNAs in the tumor tissue was demonstrated by RT-PCR, using specific sets of primers for each mRNA (Fig. 4; lanes 1–3). Two fragments were amplified by the D2R primers, corresponding to the long and short splicing variants of D2R (Fig. 4; lane 4).

**Discussion**

Gonadotroph pituitary adenomas are recognized, mostly in men and postmenopausal women, as clinically nonfunctioning sellar masses. Only seven premenopausal cases of spontaneous ovarian hyperstimulation attributable to gonadotroph macroadenoma have been reported (4–10), including a prepubertal case (7). There is only one successful postoperative pregnancy case report, which appeared while we were preparing this manuscript (10). The present report describes the first successful pregnancy after nonsurgical treatment. Moreover, this is also the first report of an FSH-producing functional pituitary microadenoma.

The most typical endocrinological abnormality in our case was the paradoxical response of FSH after TRH administration (12). As shown in the reported cases of macroadenomas, serum FSH elevation is not essential for the diagnosis of FSH-producing tumors (13). In the current case, serum FSH was mildly elevated and was not suppressed in spite of the high estradiol level.

In all previously reported cases of gonadotroph adenoma, transsphenoidal surgical resection was the first choice for treatment because of the neurological symptoms. Pituitary radiotherapy, GnRH analogs, dopamine agonist, or somatostatin analog were attempted only when patients had residual tumor or recurrent clinical symptoms. The effect of these nonoperative therapies remains controversial; and thus, there is no established treatment regimen at present (14–18). In the current case, the administration of bromocriptine, a dopamine agonist, improved the status of the hormonal levels and led to ovarian size reduction and recovery of the ovulatory cycle, followed by successful pregnancy. Although the mechanism of the effects of bromocriptine has not been clearly demonstrated, there have been some case reports in which bromocriptine was also effective for FSH-producing pituitary adenomas (19–21). Moreover, in vitro studies have shown that bromocriptine can suppress the release of gonadotropins and free α-subunits from gonadotroph tumors (22). It is also interesting that D2R gene expression was detected by *in situ* hybridization, not only in prolactinomas but also in some other kinds of pituitary tumors (23, 24). In the current case, we could demonstrate the existence of D2R mRNA in the tumor cells, in contrast with the negative results of immunohistochemistry. This may have been attributable to the differing sensitivities of the two methods or to the absence of D2R protein expression with decreased D2R gene transcription. Unfortunately, the second trial of bromocriptine administration after delivery was unsuccessful. We consider that possible bromocriptine resistance arising before the operation, down-regulation of D2R protein, or spontaneous evolution of the tumor might explain this lack of response.

In the current case, histologic evaluation revealed that PRL was also secreted in a minor population of the tumor cells. It has been pointed out that a variety of plurihormonal pituitary adenomas may exist. The hormones most commonly expressed are GH, PRL, and one or more glycoprotein hormones, most often TSH. However, FSH-or LH-secreting plurihormonal adenomas are quite rare (25–28).

In conclusion, we encountered a very rare case of FSH-secreting microadenoma, complicated with ovarian hyperstimulation and infertility. Gonadotroph adenoma with endocrinological symptoms might exist more frequently than expected, considering the recently increasing case reports thereof. Precise hormonal profiling and detailed intracranial examination are required for diagnosis. Gonadotroph adenomas may be sensitive to bromocriptine therapy via D2R, as demonstrated in the present case.

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