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CASE REPORT

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A FSH-secreting pituitary adenoma discovered after ovarian hyperstimulation syndrome: a case report, illustrating pitfalls in the interpretation of serum FSH levels

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Abstract

Background Most cases of ovarian hyperstimulation syndrome (OHSS) are caused by infertility treatment using human menopausal gonadotropin (HMG) and human chorionic gonadotropin (hCG). OHSS is widely known to have a "spoke-wheel" appearance on imaging, presenting as bilateral symmetric enlargement of ovaries with multiple cysts of varying sizes. When this spoke-wheel appearance is observed in patients not undergoing infertility treatment, tumor-derived hormones such as follicle-stimulating hormone (FSH) and hCG should be measured. However, pitfalls exist in the interpretation of FSH levels.

Case presentation A 29-year-old, gravida 0, para 0 woman visited her local doctor for irregular menstruation and to seek fertility treatment. At the first medical examination, bilateral ovarian tumors were found by ultrasonography, and she was referred to our hospital. Magnetic resonance imaging (MRI) findings of the bilateral ovarian tumors suggested typical OHSS, and thus levels of serum hormones including FSH and hCG were measured to determine whether endogenous follicle-stimulating hormones were the cause. Estradiol was elevated at 737 pg/ml (normal: 28.8-196.8 pg/ml in follicular phase) and luteinizing hormone (LH) was low at < 0.3 mIU/ml (normal: 1.4–15 in follicular phase, 2.1–88 mIU/ml in ovulatory phase). FSH (18.6 mIU/ml; normal: 3.0-14.7 in follicular phase, 4.5–22.5 mIU/ ml) and hCG (< 1.0 mIU/ml) were within normal ranges for non-pregnant women. Initially, since ovarian neoplasms producing estrogen were suspected, surgical resection was scheduled. However, computed tomography of the neck to pelvic region was performed to rule out metastatic ovarian tumors, and indicated a coincidental pituitary lesion, which was pathologically characterized as an FSH-secreting pituitary adenoma. Consequently, the final diagnosis was OHSS caused by an FSH-producing pituitary adenoma and the scheduled ovarian surgery was avoided.

Conclusions Awareness of MRI findings of OHSS is important to avoid unnecessary invasive procedures. When treating patients who have suspected OHSS on imaging but whose serum FSH is in the normal range, it is also

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important to know that an unsuppressed FSH level despite the negative feedback effect of high estrogen should prompt investigation for a pituitary adenoma as a primary consideration.

Keywords Magnetic resonance imaging, Ovarian hyperstimulation syndrome, OHSS, Pituitary adenoma, Case report

Background

Ovarian hyperstimulation syndrome (OHSS) is known to be caused by endogenous hormones, such as tumor-derived hormones, in the absence of infertility treatment, but most cases of OHSS are caused by infertility treatment using human menopausal gonadotropin (HMG) and human chorionic gonadotropin (hCG) [1]. OHSS is widely known to show a "spoke-wheel" appearance on imaging, presenting as bilateral symmetric enlargement of ovaries with multiple cysts of varying sizes [2]. When this spoke-wheel appearance is observed in patients not undergoing infertility treatment, tumor-derived hormones such as follicle-stimulating hormone (FSH) and hCG should be measured.

Here we report the case of a reproductive-age woman showing OHSS on imaging who was not undergoing fertility treatment. Since serum levels of FSH and hCG were in normal ranges, OHSS due to an FSH-secreting tumor was thought to be unlikely. As a result, it took a long 4 months to discover an FSH-secreting pituitary adenoma. This case illustrates pitfalls in the interpretation of serum FSH level, especially when it is within the normal range. Therefore, we describe the relationship between endogenous OHSS and serum hormone levels, with discussion of previous reports.

Case presentation

A 29-year-old Japanese woman (G0 P0) visited her local doctor with chief concerns of irregular menstruation and seeking fertility treatment. She was suspected of having bilateral ovarian tumors, and was referred to our hospital.

Three years prior, she visited another hospital after feeling a tumor in the right lower abdomen and was diagnosed with large 8-cm cystic masses in both ovaries. Serum LH, FSH, hCG and testosterone levels were measured and were all within normal ranges. The diagnosis was hypothalamic menstrual irregularity due to emaciation, and the patient was treated with Kaufman therapy, but did not visit the gynecologist after that. One and a half years later, left ovarian torsion occurred, and she underwent ovarian de-torsion and ovarian drilling at her local doctor.

Pelvic 1.5-tesla (T) MRI demonstrated bilateral ovarian masses (right 9.2 cm, left 8.7 cm) including multiple large follicle-like cysts showing low signal on T1-weighted and high signal on T2-weighted images (Fig. 1a, b). The uterine wall showed edematous thickening on T2-weighted images (Fig. 1a). Cyst walls were uniformly enhanced on contrast-enhanced fat-suppressed T1-weighted images (Fig. 1c), and no solid component was observed in the cysts. No abnormal diffusion restriction was observed in masses in either ovary on diffusion-weighted image ($b=1000$ s/mm^2) (Fig. 1d). Ovarian hyperstimulation syndrome (OHSS) was suspected based on the morphology of the cystic lesions, which is known as the appearance of spokes of a wheel on the bilateral ovaries.

Blood tests showed elevated E2 of 737 pg/ml (normal: 28.8-196.8 pg/ml in follicular phase) and decreased LH < 0.3 mIU/ml (normal: 1.4–15 in follicular phase, 2.1–88 mIU/ml in ovulatory phase). FSH (18.6 mIU/ml; normal: 3.0-14.7 in follicular phase, 4.5–22.5 mIU/ ml), hCG (< 1.0 mIU/ml), PRL (30.4 ng/ml; normal: 4.91–29.32 ng/ml) and thyroid-stimulating hormone (TSH) (1.84 mIU/L; normal: 0.4-4.0 mIU/L) were within normal limits. Since FSH and hCG, which can stimulate ovarian follicles and swell bilateral ovaries, were in normal ranges, an endocrinologist interpreted this result as indicating hyperestrogenemia produced by ovarian tumors causing negative feedback effect on LH secretion. Therefore, the possibility of estrogen-producing ovarian neoplasms could not be ruled out, and gynecological surgery was scheduled.

When a whole-body CT was performed to exclude metastatic ovarian tumors before surgery, a tumor was noted in the pituitary gland (Fig. 2a). A pituitary adenoma invading the left cavernous sinus was detected on 1.5-T brain MRI of the pituitary gland (Fig. 2b), and a transsphenoidal sinus pituitary tumor was resected. Complete resection of the pituitary adenoma was abandoned due to persistent bleeding from the cavernous sinus. Pathologically, the pituitary tumor cells showed a pseudorosette arrangement with vasocentricity (Fig. 3), and were FSH-positive and LH-negative on immunostaining, leading to the diagnosis of FSH-producing pituitary adenoma.

Brain MRI revealed the tumor size had decreased from $40 \times 20 \times 19$ mm to $23 \times 19 \times 19$ mm four months after the surgery (Fig. 4).

One month after the surgery, serum estrogen was within the normal limit and FSH also decreased to 5.3 mIU/ml. The patient resumed normal menstrual cycles two months later. LH started to increase 5 months after the surgery (Table 1). Six months after the surgery, transvaginal ultrasound showed that the long diameter of both ovaries had shrunk from about 9 cm to approximately 6 cm (Fig. 5).

The patient and her husband underwent a thorough examination at the infertility treatment clinic. One round

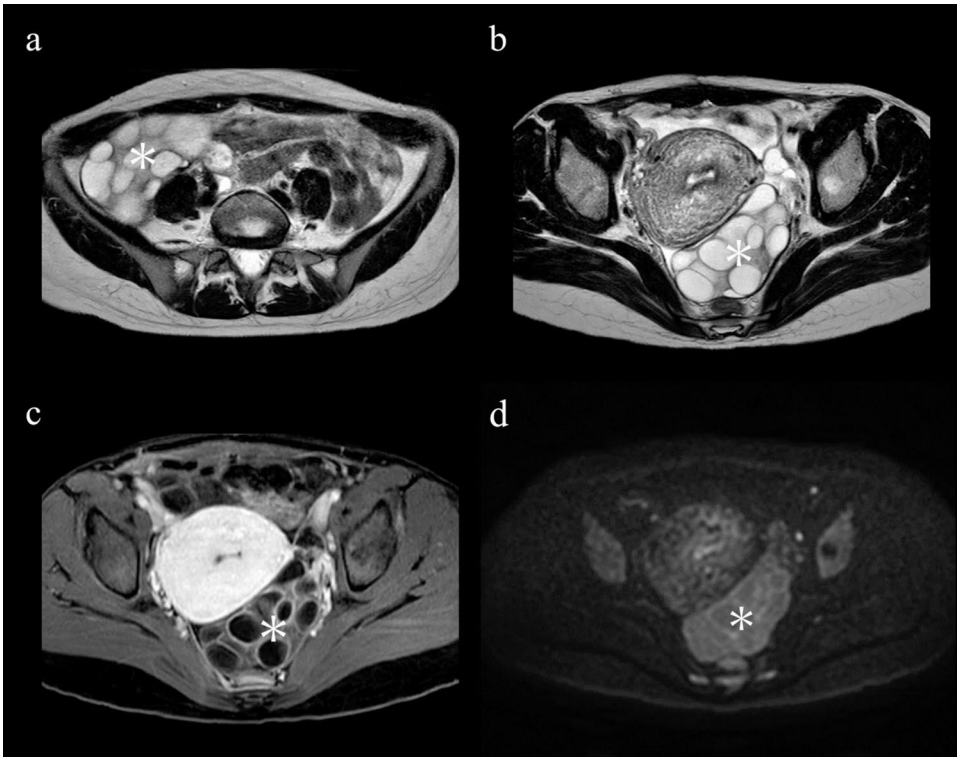

Fig. 1 On T2-weighted images (spin echo; repetition time [TR]/echo time [TE], 4500/100 ms), the right ovary was swollen to 9.2 cm (**a**: *) and the left ovary to 8.7 cm (**b**: *) in maximum diameter. Both were accompanied by multiple large follicle-like cysts. The uterine wall showed edematous thickening. Cyst walls were uniformly enhanced on contrast-enhanced fat-suppressed T1-weighted images (gradient echo; TR/TE, 5.8/1.86 ms) (**c**: *), and no solid component was observed in the cysts. No abnormal diffusion restriction was observed in masses in either ovary on diffusion-weighted image (b = 1000 s/mm^2, TR/TE, 4359/78 ms) (d: *)

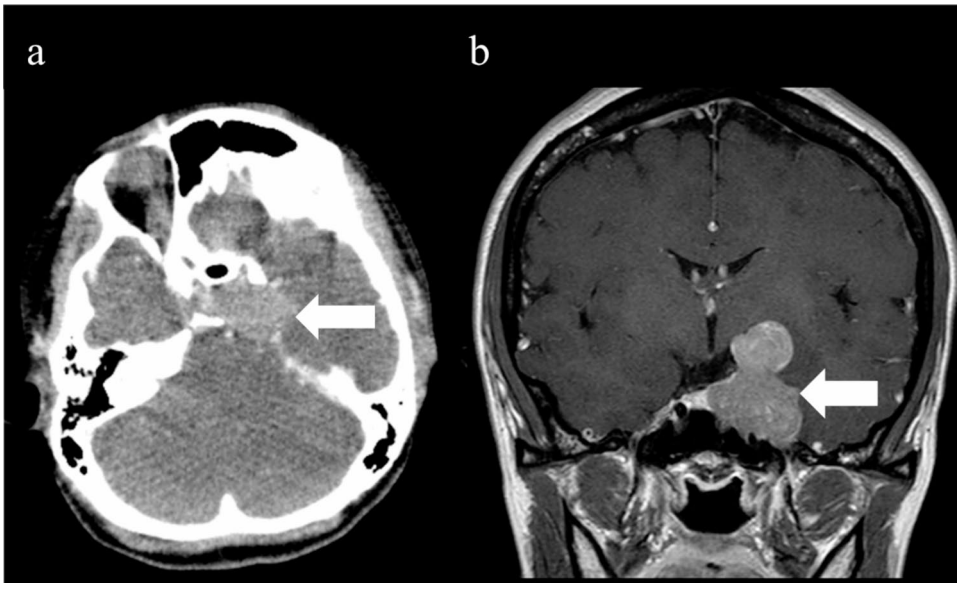

Fig. 2 CT revealed a mass in the left side of the sella turcica (**a**: arrow). Coronal contrast-enhanced T1-weighted images of the pituitary gland revealed the mass as a pituitary adenoma invading the left cavernous sinus and displacing the left temporal lobe (gradient echo; TR/TE, 20/4.82 ms) (**b**: arrow)

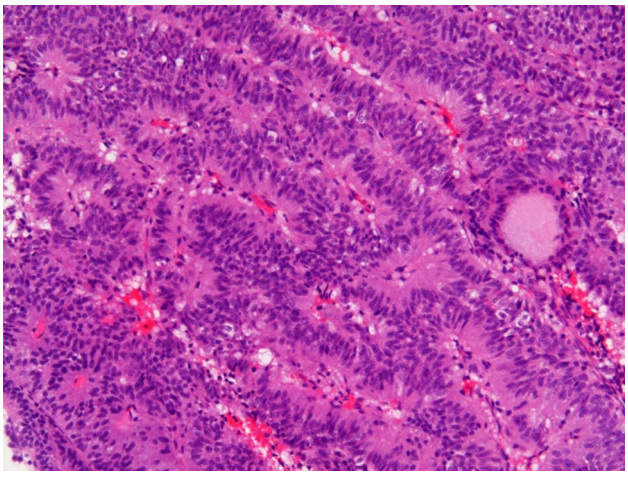

Fig. 3 Tumor cells show a pseudorosette arrangement with vasocentricity

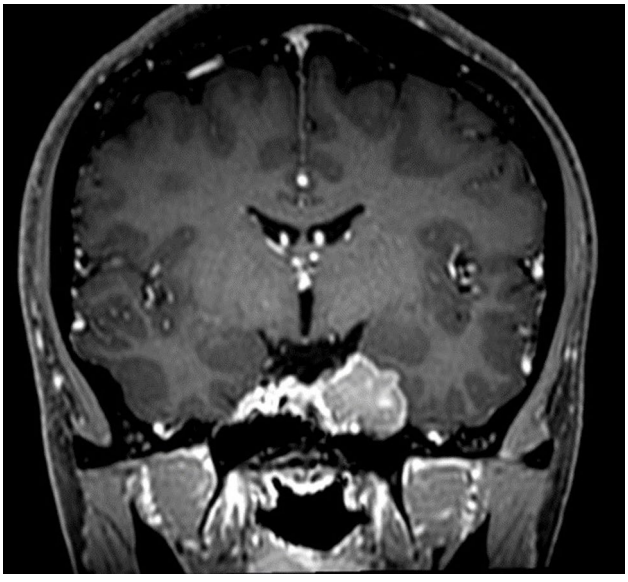

Fig. 4 Four months after the surgery, brain MRI revealed the tumor size had decreased from 40 × 20 × 19 mm to 23 × 19 × 19 mm

of intracytoplasmic sperm injection was performed, but she has not become pregnant.

Discussion

In general, OHSS is a complication sometimes seen in patients receiving HMG-hCG therapy for infertility [3]. Other endogenous diseases including hypothyroidism, FSH receptor mutations, polycystic ovary syndrome (PCOS) [4–6], and FSH-secreting pituitary adenomas can also cause persistent OHSS [7].

Based on MR findings, this case was considered to be OHSS due to an FSH and/or hCG-secreting tumor somewhere else in the body. However, the diagnosis was difficult to reach and it took more than four months to find the FSH-secreting pituitary adenoma because serum levels of FSH and hCG were within the normal range, which seemed to suggest that the bilateral ovarian masses were not associated with hormonal stimulation by tumors elsewhere. The rarity of FSH-producing pituitary adenomas also contributed to the delayed diagnosis. These facts were critical pitfalls in the clinical diagnosis.

Pituitary gonadotrophin-producing tumors account for 40% of macroadenomas. However, most of them are non-functional because they produce only parts of the hormone, either the alpha or beta subunits. In contrast, pituitary adenomas producing a functional, fully circulating protein are rare, accounting for less than 1% of all pituitary adenomas [8]. Thus, most pituitary adenomas do not produce enough hormone to cause menstrual abnormalities or OHSS, and even large pituitary adenomas producing FSH and LH rarely present with such symptoms associated with OHSS [9]. FSH-producing tumors are generally described as having elevated FSH, low LH, and elevated E2, although FSH levels may be within the normal range [10–13] or elevated to the upper limit of the reference range [7, 9, 14] and E2 may be within the normal range [9] in patients of reproductive age. In an environment of very high estrogen levels, negative feedback suppresses FSH and LH secretion from the normal pituitary tissue. In the presence of an FSH-producing tumor, negative feedback due to elevated E2 from tumor-produced FSH also occurs, resulting in

Table 1 Changes in blood hormone levels before and after surgery for FSH-producing pituitary adenoma

Month	-5	-4	-3	-1	0	1	2	5
TSH (mIU/L)	—	—	1.84	1.32		1.79	0.99	2.36
LH (mIU/ml)	< 0.3	< 0.3	< 0.3	< 0.3		< 0.3	< 0.3	0.4 ↑
FSH (mIU/ml)	15.7	15.9	18.6	23.1	Surgery	5.3 ↓	4.7	5.6
PRL (ng/ml)	—	41.1	30.4	34.8		31.5	—	—
E2 (pg/ml)	569	419	737	—		56.9 ↓	47.8	118

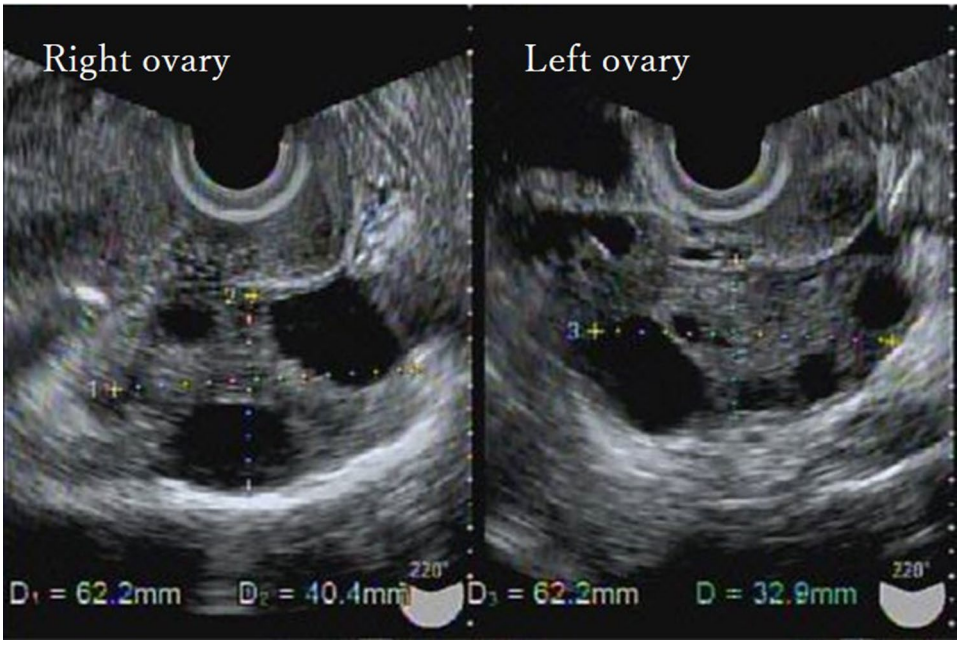

Fig. 5 Six months after the surgery, transvaginal ultrasound showed that the long diameter of both ovaries had shrunk to approximately 6 cm

suppression of FSH and LH production by the normal pituitary gland. However, FSH, which is constantly produced by the tumor, is not suppressed. This results in a mismatch where LH falls below the reference value but FSH does not. According to a systematic review including 50 patients with OHSS induced by gonadotroph pituitary adenoma, mean FSH level was in the normal range (14.4 IU/l) and estradiol level was high in 82% of patients, exceeding 350 pg/mL, similarly to this case. Consequently, the possibility of an FSH-producing tumor must be considered even when FSH is in the normal range. In this case, LH was suppressed due to the high level of E2 produced by bilateral swollen ovaries, but the fact that FSH was not suppressed to below the reference range should have been considered inconsistent with findings suggestive of an E2-producing ovarian tumor.

In previous reports, some patients underwent surgery based on a mistaken diagnosis of serous cystadenoma or ovarian enlargement refractory to hormone therapy despite having endogenous OHSS [14]. Surgery was also performed due to adnexal torsion associated with OHSS [10, 12], which was seen in the past medical history of this case, and may also manifest as worsened abdominal pain [11]. In our case, surgery for ovarian masses was scheduled because the possibility of an ovarian tumor was suspected before the diagnosis of endogenous OHSS was established. Although surgery was not performed because a pituitary lesion was detected on preoperative CT, an invasive procedure might have been performed if the lesion had not been found. As such, a correct diagnosis of OHSS by MRI was important to avoid unnecessary invasive procedures.

Conclusion

Awareness of MRI findings of OHSS is important to avoid unnecessary invasive procedures. When treating patients who have suspected OHSS on imaging but whose serum FSH is in the normal range, it is also important to know that an unsuppressed FSH level despite the negative feedback effect of high estrogen should prompt investigation for a pituitary adenoma as a primary consideration.

Abbreviations

OHSS	Ovarian Hyperstimulation Syndrome
HMG	Human Menopausal Gonadotropin
hCG	Human Chorionic Gonadotropin
FSH	Follicle-Stimulating Hormone
G	Gravida
P	Para
LH	Luteinizing Hormone
E2	Estradiol
RI	Magnetic Resonance Imaging
CT	Computed Tomography
T	Tesla
TSH	Thyroid-Stimulating Hormone

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KY and GN contributed to writing the manuscript. HM contributed to correcting the patient's data for the work. MO contributed to the patient's treatment. TY performed postoperative histological examination. KY contributed to the acquisition of MRI data. KO contributed to revising the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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