www.nature.com/clinicalpractice/endmet

Ovarian hyperstimulation syndrome caused by an FSH-secreting pituitary adenoma

Odelia Cooper, Jordan L Geller and Shlomo Melmed*

SUMMARY

Background A 40-year-old woman presented with galactorrhea and oligomenorrhea. She had a history of multiple ovarian cysts and pelvic pain.

Investigations Laboratory evaluation included measurements of the levels of estradiol, follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, free endogenous T_4, the glycoprotein hormone α subunit, cortisol, adrenocorticotropic hormone, and insulin-like growth factor I. Radiological studies included MRI of the pituitary.

Diagnosis Ovarian hyperstimulation syndrome caused by a pituitary adenoma, secreting follicle-stimulating hormone.

Management The patient underwent trans-sphenoidal resection of the adenoma, with subsequent normalization of hormonal values and symptoms.

KEYWORDS clinically nonfunctioning adenoma, follicle-stimulating hormone, gonadotrope adenoma, hypersecretion, ovarian hyperstimulation syndrome

CME

O Cooper is a Research Fellow in Endocrinology, JL Geller is a Clinical Endocrinologist and S Melmed is the Director of the Burns and Allen Research Institute and Senior Vice President of Academic Affairs, all at the Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Correspondence
*Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 2015, Los Angeles, CA 90048, USA
melmed@csmc.edu

Received 19 October 2007 **Accepted** 8 January 2008 **Published online** 12 February 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpendmet0758

Vanderbilt Continuing Medical Education online
This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

Competing interests
The authors declared no competing interests.

THE CASE

A 40-year-old woman presented in 2006 with a 15-year history of bilateral galactorrhea. She has never been pregnant and had initially presented at the age of 25 years with menometrorraghia (dysfunctional uterine bleeding) and bilateral galactorrhea, while being on oral contraceptives. At that time investigations revealed the presence of benign luteinized follicular cysts, which were resected laparoscopically. Her symptoms then temporarily abated, but recurred with re-growth of ovarian cysts and with features of the ovarian hyperstimulation syndrome (OHSS) including pelvic pain and enlarged, multicystic ovaries, which required three separate operations over the following 5 years.

The patient was referred for endocrinological evaluation in 2006, because she had persistent galactorrhea. At this time, she reported having had a normal adrenarche and puberty, and she denied suffering from headaches, visual disturbances, weight or body habitus changes, polyuria, hirsutism or acne. Her history revealed that she was receiving the oral contraceptive pill. On physical examination, she was found to have bilateral galactorrhea.

Biochemical testing demonstrated a negative pregnancy test, prolactin levels of 3,000 pmol/l (reference range 165–1,009 pmol/l), follicle-stimulating hormone (FSH) levels of 19.2 IU/l (reference range 4–13 IU/l), luteinizing hormone (LH) levels of 0.6 IU/l (reference range 1–18 IU/l), estradiol levels of 3,851.0 pmol/l (reference value <1,094.0 pmol/l), adrenocorticotropic hormone levels of 2.9 pmol/l (reference range 1.1–5.9 pmol/l), 0800 h cortisol levels of 510.4 nmol/l (reference range 165.5–634.6 nmol/l), glycoprotein hormone α subunit levels of 0.8 μg/l (reference

range 0.04–0.38 μg/l), TSH levels of 3.3 mIU/l (reference range 0.39–4.6 mIU/l), free endogenous T_4 levels of 11.6 pmol/l (reference range 10.3–34.7 pmol/l), and insulin-like growth factor I levels of 33.7 nmol/l (reference range 18.1–53.7 nmol/l). MRI of the pituitary gland revealed a 16 × 27 × 22 mm pituitary adenoma with suprasellar extension, elevation and compression of the optic chiasm, and extension to the right cavernous sinus (Figure 1). The patient underwent trans-sphenoidal resection of the pituitary mass.

Immunohistochemical staining of the pituitary adenoma specimen was positive for α subunit, FSHβ subunit and LHβ subunit; staining was negative for growth hormone, prolactin, adrenocorticotropic hormone and for TSH. The Ki-67 proliferative index, measuring the growth fraction of tumor cells, was low (1%) and almost no cells showing overexpression of p53 protein were detected. These findings generally suggests a low tumor grade and a good prognosis.

The patient was diagnosed as harboring a gonadotrope cell adenoma with secondary ovarian hyperstimulation. Postoperatively, galactorrhea resolved, and normal menses resumed. Anterior pituitary hormone reserve was intact.

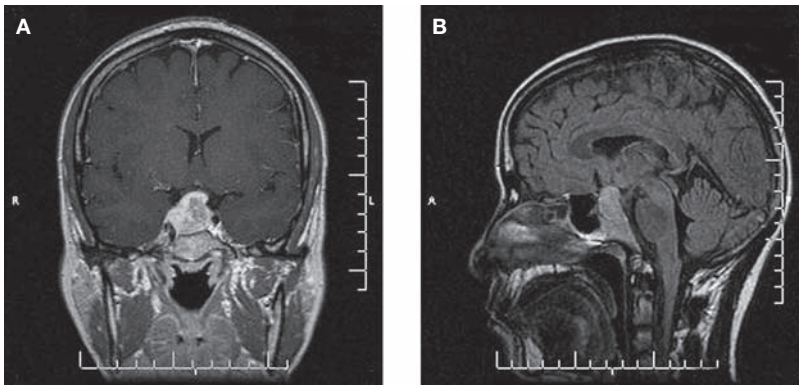

Figure 1 The patient's pre-operative MRI depicting the pituitary mass. (**A**) Coronal view and (**B**) sagittal view.

DISCUSSION OF DIAGNOSIS

This case typifies the presentation of OHSS in the face of an FSH-secreting adenoma. OHSS comprises extravasation of fluid into the peritoneal cavity, with consequent ascites, hemoconcentration, and electrolyte abnormalities. When OHSS is caused by an FSH-secreting adenoma, FSH levels are usually elevated, LH is suppressed, and estradiol levels are elevated up to 80 times the normal levels. Women suffering from OHSS usually develop enlarged multicystic ovaries associated with abdominal pain. The detection of elevated prolactin levels then triggers the ordering of a pituitary MRI, which will reveal the presence of a pituitary adenoma. In general, women with FSH-secreting tumors are asymptomatic, and often FSH levels are only marginally above the normal range for reproductive-age women. Gonadotropin-secreting adenomas are more common in postmenopausal women, who are relatively insensitive to ovarian hyperstimulation.[1]

Gonadotropinomas account for 15–40% of all pituitary tumors. More than 80% of clinically nonfunctioning pituitary adenomas are estimated to be gonadotrope-derived, accounting for approximately half of all macroadenomas. These adenomas often arise in middle-aged men, who may have low testosterone levels with high LH and FSH levels, suggesting a diagnosis of primary hypogonadism. There are also a few reports of male gonadotropinomas leading to elevated testosterone levels resulting in an increased sperm count, and, in addition, there is a case report of a 7-year-old boy who developed precocious puberty as a consequence of a gonadotropin-secreting adenoma.[2,3] Women with intact gonadotrope adenomas and supranormal FSH levels are generally not recognized as exhibiting a syndrome, because many are over 45 years of age with ovaries devoid of pre-antral follicles, and are insensitive to the action of FSH.[4] These gonadotrope adenomas are, therefore, more difficult to diagnose in women who are perimenopausal or postmenopausal.[5]

In women, gonadotropinomas should also be considered if there is a history of headaches or visual changes. Measurements of basal FSH, LH, and α subunit levels may aid the diagnosis, as supra-normal α subunit levels with intact LH and FSH levels, or with disproportionate FSH and LH levels, suggest the presence of a gonadotropinoma, especially when the hormone subunits are induced by a TRH (TSH-releasing hormone) stimulation test. Administration of TRH rarely enhances gonadotropin or gonadotropin subunit secretion in healthy individuals, whereas it can enhance subunit secretion in up to 70% of patients with gonadotropinomas. Although LHβ is the gonadotropin subunit most sensitive to increase on administration of TRH, there is currently no standard commercial assay for measuring the LHβ subunit, making this protein impractical for routine use.[5]

Clinical and biological behavior of gonadotropinomas has been gleaned from *in vitro* studies and from limited case reports and case series. Gonadotropinomas exhibit variable degrees of differentiation. Only up to 15% of tumor cells—grouped in small islets around blood vessels in the tumor parenchyma—show immunohistochemical staining (of variable intensity), which could explain the low levels of circulating hormone concentrations. Nonfunctioning gonadotropinomas are mainly composed of tumor cells with negative immunostaining for all pituitary hormone antibodies, but these tumor cells usually stain positively for the DAX-1 (Nuclear receptor subfamily 0 group B member 1) protein, which regulates gonadotrope differentiation.[5]

The bioactivity and concentration of baseline serum FSH are higher in patients with adenomas than in controls. In addition, bioactive and immunoreactive FSH levels increase in response to the administration of TRH in patients with adenomas. The cellular machinery for biosynthesis and processing of FSH is intact, and functional FSH is secreted despite aberrant tumor growth.[6] It should, however, be mentioned that the unassociated LHβ and FSHβ subunits exhibit no intrinsic biological activity and that formation of a heterodimer with the α subunit is essential for biological activity. As 70–100% of nonfunctioning adenomas secrete free subunits, these tumors usually show no biological activity.[7]

In a subject with an intact pituitary gland, one would expect that high estradiol levels would suppress gonadotropin-releasing hormone (GnRH) and, therefore, suppress gonadotropin secretion. In gonadotrope adenomas, however, the normal feedback system is impaired, thereby permitting the presence of persistently elevated FSH and estradiol levels, which then leads to the symptoms and signs of OHSS.

Clinical behavior of gonadotropinomas has been described in a number of case series, including an analysis of 100 patients with gonadotropin-positive pituitary adenomas reported between 1976 and 1992.[8] In this report, gonadotropin levels were found to be inappropriately low compared with the expected levels in postmenopausal women.[8] LH concentrations were elevated in 36% of males, with 9% showing LH hypersecretion (defined as more than a two-fold increase above the upper limit of normal). FSH levels were elevated in 42% of males, with FSH hypersecretion reported in 19%. Levels of α subunit were high in only 1 of 29 patients. In other case series, however, α subunit levels were elevated in 15–32% of patients.[9–11] Hypogonadism was diagnosed biochemically in 78% of males.[8] These patients presented with mass effect symptoms including loss of vision, symptoms of hypopituitarism, and headaches.[8]

On electron microscopy, gonadotrope adenomas showed a gender-related ultrastructural dimorphism. In men, gonadotrope adenomas tend to have small cells with decreased cytoplasmic volume densities of endoplasmic reticulum and Golgi membranes, and with variable numbers of secretory granules. On the other hand, in women gonadotrope adenomas have a well-developed endoplasmic reticulum, a 'honeycomb' Golgi complex and sparse, small secretory granules. Using this distinction, 45% of the adenomas in this series were structurally classified as 'male' gonadotrope adenomas whereas 9% were 'female' adenomas.[8]

Hypersecretion of gonadotropins and their subunits rarely leads to a defined clinical syndrome, unlike syndromes associated with prolactin or growth hormone hypersecretion. Consequently, most gonadotropinomas have, heretofore, been classified as nonfunctioning or 'null cell' adenomas. It is known, however, that gonadotropinomas often secrete α subunit, FSH and FSHβ subunit as well as LH and LHβ subunit. In fact, the 2004 WHO classification of pituitary tumors places gonadotrope adenomas in their own class, as it has now become clear that gonadotrope cells of the anterior pituitary pursue a pathway of differentiation distinct from other tropic hormone cells. Unlike 'null cell' adenomas, gonadotropinomas express the nuclear receptor steroidogenic factor-1 almost exclusively in cells that produce gonadotropin β subunits; moreover, this factor has been shown to regulate glycoprotein hormone α subunit gene expression in pituitary gonadotrope cells.[12]

Patients may present with symptoms of excess gonadotropin secretion leading to the syndrome of ovarian hyperstimulation. The pathogenesis of this syndrome has been explored in an animal model in which transgenic mice with pituitary-directed hypersecretion of LH developed multicystic ovaries. These mice had an increased pituitary size and showed proliferation of Pit-1 (pituitary-specific positive transcription

factor 1)-positive cells that culminated in the appearance of functional pituitary adenomas. It is thought that LH could be an extrinsic factor acting through the ovary leading to the formation of functional pituitary adenomas.[13]

OHSS has been reported in patients aged 10–39 years, with pituitary tumors varying in size from 8 mm diameter to huge invasive adenomas. As in the case presented here, premenopausal women with FSH-secreting tumors may harbor a clinically functioning adenoma, manifesting with enlarged multicystic ovaries and with abdominal pain. Similar cases in the literature are summarized in Supplementary Tables 1–3.

DIFFERENTIAL DIAGNOSIS

OHSS can occur in association with other disease states. Patients with polycystic ovary syndrome who become pregnant are at risk of OHSS as they have multiple partially stimulated antral follicles, which can over-respond to exogenous gonadotropins as reported during assisted reproductive treatment. OHSS has also been reported in association with primary hypothyroidism, possibly caused by TSH-mediated stimulation of the FSH receptor or by enhanced TRH production stimulating gonadotropin release. In addition, a single patient with bilateral granulosa cell tumors has been reported to have developed OHSS.[14]

TREATMENT AND MANAGEMENT

Surgical resection is the definitive and primary therapy for OHSS due to gonadotropin-secreting adenomas. Surgery results in normalization of gonadotropin and estradiol levels. Menstrual cycles resume and the ovaries revert to normal size with cyst remission. In those with recurrent tumors, radiation therapy may be required.

Medical therapies are generally not effective. In theory, one possible medical treatment would be the administration of a GnRH analog which would decrease FSH levels, thereby leading to resolution of OHSS; however, reports have actually shown a paradoxical increase in gonadotropin secretion in response to this treatment,[4,15–20] and in one case OHSS was induced after initiation of GnRH therapy with dramatic increases in FSH and estradiol levels.[21]

There are three reports of patients with OHSS who were initially treated medically. These patients presented with oligomenorrhea, abdominal distension, and enlarged multicystic ovaries. Estradiol levels were as high as 6,755 pmol/l, with elevated prolactin and FSH levels and suppressed LH levels. The three patients were treated with a dopamine agonist and two of the patients also received medroxyprogesterone. Ovarian volumes and hormonal values normalized. Eventually, however, the adenomas continued to grow and were resected, showing positive immunostaining for LH in two cases and for FSH in one case.[15,22]

After resection of a pituitary adenoma, patients are monitored annually with MRI, looking for evidence of a possible recurrence. Patients should also undergo hormonal testing 3 months after surgery to assess whether hypopituitarism is present. If there is evidence of a deficiency of any of the hormones of the pituitary axis, hormonal replacement therapy is initiated.

CONCLUSIONS

We present a case of a woman who developed OHSS due to an FSH-secreting pituitary adenoma. This syndrome comprises enlarged, multicystic ovaries, oligomenorrhea or amenorrhea, elevated estradiol levels and, usually, elevated serum FSH levels. After resection of the pituitary adenoma, the endocrine profile and symptoms revert to normal.

Our case brings to light two instructive points. Firstly, contrary to the assumption that gonadotrope adenomas are clinically nonfunctioning adenomas, FSH-secreting adenomas may in fact be functional, leading to hypersecretory symptoms as in the development of OHSS. Secondly, when clinicians encounter patients presenting with symptoms of abdominal pain, abnormal menses and multicystic ovaries, they should measure estradiol and gonadotropin levels to exclude OHSS caused by a pituitary adenoma. In our case, the patient had a 15-year history of such symptoms but had not undergone an endocrine work-up, which could have revealed the presence of a pituitary adenoma during that period. Clinical awareness and an appropriate endocrine work-up facilitate early diagnosis and treatment of this syndrome, thereby avoiding multiple therapeutic procedures for ovarian cysts and ultimately also restoring fertility.

Supplementary information in the form of three tables, listing similar cases described in the literature, is available on the *Nature Clinical Practice Endocrinology & Metabolism* website.

Acknowledgments

This work was supported by NIH grants T32 DK007770-06A2 and CA75979. Consent for the publication of Figure 1 was obtained from the patient.

Competing interests

The authors declared no competing interests.

References

1 Roberts JE *et al*. (2005) Spontaneous ovarian hyperstimulation caused by a follicle-stimulating hormone-secreting pituitary adenoma. *Fertil Steril* **83:** 208–210
2 Zarate A *et al*. (1986) Gonadotropin-secreting pituitary adenoma with concomitant hypersecretion of testosterone and elevated sperm count. Treatment with LRH agonist. *Acta Endocrinol* **113:** 29–34
3 Ambrosi B *et al*. (1990) Precocious puberty in a boy with a PRL-, LH- and FSH-secreting pituitary tumor: hormonal and immunocytochemical studies. *Acta Endocrinol* **122:** 569–576
4 Pentz-Vidovic I *et al*. (2000) Evolution of clinical symptoms in a young woman with a recurrent gonadotroph adenoma causing ovarian hyperstimulation. *Eur J Endocrinol* **143:** 607–614
5 Chaidarun SS and Klibanski A (2002) Gonadotropinomas. *Semin Reprod Med* **20:** 339–348
6 Galway AB *et al*. (1990) Gonadotroph adenomas in men produce biologically active follicle-stimulating hormone. *J Clin Endocrinol Metab* **71:** 907–912
7 Melmed S (2002) *The Pituitary.* Cambridge: Blackwell Science
8 Young W *et al*. (1996) Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. *Mayo Clin Proc* **71:** 649–656
9 Beck-Peccoz P *et al*. (1992) Glycoprotein hormone α-subunit in pituitary adenomas. *Trends Endocrinol Metab* **3:** 41–45
10 Oppenheim DS *et al*. (1990) Prevalence of α-subunit hypersecretion in patients with pituitary tumors: clinically nonfunctioning and somatotroph adenomas. *J Clin Endocrinol Metab* **70:** 859–864
11 Nobels FR *et al*. (1993) A comparison between the diagnostic value of gonadotropins, α subunit, and chromogranin-A and their response to thyrotropin-releasing hormone in clinically nonfunctioning, α subunit-secreting, and gonadotroph pituitary adenomas. *J Clin Endocrinol Metab* **77:** 784–789
12 Asa SL *et al*. (1996) The transcription activator steroidogenic factor-1 is preferentially expressed in the human pituitary gonadotroph. *J Clin Endocrinol Metab* **81:** 2165–2170
13 Mohammad HP *et al*. (2003) Targeted overexpression of luteinizing hormone causes ovary-dependent functional adenomas restricted to cells of the Pit-1 lineage. *Endocrinology* **144:** 4626–4636
14 Segal R *et al*. (1995) Clinical review of adult granulosa cell tumors of the ovary. *Gynecol Oncol* **56:** 338–344
15 Murata Y *et al*. (2003) Successful pregnancy after bromocriptine therapy in an anovulatory woman complicated by follicle-stimulating hormone-producing plurihormonal pituitary microadenoma. *J Clin Endocrinol Metab* **88:** 1988–1993
16 Christin-Maitre S *et al*. (1998) A spontaneous and severe hyperstimulation of the ovaries revealing a gonadotroph adenoma. *J Clin Endocrinol Metab* **83:** 3450–3453
17 Maruyama T *et al*. (2005) Follicle stimulating hormone-secreting pituitary microadenoma with fluctuating levels of ovarian hyperstimulation. *Obstet Gynecol* **105:** 1215–1218
18 Kihara M *et al*. (2006) Ovarian hyperstimulation caused by gonadotroph cell adenoma: a case report and review of the literature. *Gynecol Endocrinol* **22:** 110–113
19 Berezin M *et al*. (1984) Reduction of follicle-stimulating hormone (FSH) secretion in FSH-producing pituitary adenoma by bromocriptine. *J Clin Endocrinol Metab* **59:** 1220–1223
20 Yamakita N *et al*. (1999) Reduction of plasma gonadotropin levels and pituitary tumor size by treatment with bromocriptine in a patient with gonadotropinoma. *Intern Med* **38:** 266–271
21 Castelbaum AJ *et al*. (2002) Exacerbation of ovarian hyperstimulation by leuprolide reveals a gonadotroph adenoma. *Fertil Steril* **78:** 1311–1313
22 Knoepfelmacher M *et al*. (2006) Effectiveness of treating ovarian hyperstimulation syndrome with cabergoline in two patients with gonadotropin-producing pituitary adenomas. *Fertil Steril* **86:** e15–e18