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Case report

Functional gonadotroph pituitary adenoma: A case report☆

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ABSTRACT

Most clinically non-functioning pituitary tumour arise from gonadotroph cells. However, clinically functional pituitary gonadotroph adenoma is rare. Here we report a female case who presented with menstrual disturbances, however further workup demonstrated a pituitary microadenoma with elevated FSH and oestradiol level. Transsphenoidal resection was performed and the surgical histopathology confirmed pituitary gonadotroph adenoma. Postoperatively, improvement in both symptoms and hormonal profile were observed. Interestingly, the initially enlarged and polycystic ovaries became within normal range around eight months after the surgery. We suggest functional gonadotroph adenoma should be considered in the presence of gynaecological disorder with persistently elevated oestradiol and FSH levels.

1. Introduction

Although gonadotroph tumours account for approximately 40 % of all resected pituitary neuroendocrine tumours (PitNETs), they are often clinically nonfunctional. A functional gonadotroph adenoma is a rare type of PitNET that results in over-secretion of gonadotropin, which leads to elevated oestrogen levels in woman or elevated testosterone levels in man. The main clinical manifestations in male patients are testicular hypertrophy and/or sexual dysfunction, while the main manifestation in children is precocious puberty. The over-secretion of gonadotropin caused clinical manifestations in female patients, such as irregular menstrual period, oligomenorrhea, secondary amenorrhea, abnormal uterine bleeding, and infertility, often lead to the diagnosis of polycystic ovary syndrome, or ovarian hyperstimulation syndrome. Because of these atypical gynaecological symptoms, functional gonadotroph adenoma in female patient are often misdiagnosed, or delayed diagnosed until patients present with mass effect or hypopituitarism

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symptoms. The present report describes a young woman with a functional gonadotroph adenoma. Her clinical characteristics and treatment are analysed and are herein summarised to improve clinicians' understanding of this rare disease, and therefor to avoid irreparable damage to patients from misdiagnosis and delayed treatment.

2. Case report

A 20-year-old woman presented to our gynaecology department for evaluation of menstrual disturbances. Her menarche was at age of 13, her menstrual period has been regular until age of 17, at that time, she started having irregular menstrual period, oligomenorrhea and later secondary amenorrhea for unclear reason. She was unmarried, had no children, had no sexual life history, and had not used contraceptives previously. The patient was 1.65 m tall, weighted 50 kg and had a body mass index of 18.5 kg/m^2. The patient has normal breast development, no galactorrhea, no acne, no increased body hair, and no acanthosis nigricans. On Jun 8, 2019, abdominal ultrasonography showed that both ovaries were enlarged (left ovary: 5.0 × 5.8 cm, right ovary: 4.4 × 5.2 cm) and polycystic. Endocrine examination showed high levels of follicle-stimulating hormone (FSH, 12.7 mIU/ml; reference range 3.5–12.5 mIU/ml) and oestradiol (496.7 pg/ml; reference range 12.4–233.0 pg/ml), a low level of luteinising hormone (LH, 0.2 mIU/ml; reference range 2.4–12.6 mIU/ml), and a slightly elevated level of prolactin (PRL, 17.6 ng/ml; reference range 4.8–23.3 ng/ml). The patient later visited the gynaecology department numerous times for repeat examinations. Endocrine examination showed that the levels of FSH and oestrogen gradually increased; in particular, the oestrogen level more obviously increased and fluctuated within a wider range. On August 8, 2022, abdominal ultrasonography showed that both ovaries had gradually become enlarged (left ovary: 5.1 × 6.1 cm, right ovary: 4.6 × 6.6 cm). In August 2022, skull magnetic resonance imaging (MRI) showed a pituitary tumour. The tumour was approximately 9.9 × 8.9 × 9.4 mm in size and exhibited uniform enhancement. [Fig. 1(A-C)]. In September 2022, the patient was admitted to the neurosurgery department. Physical examination showed no neurological dysfunction. A discussion took place among a multidisciplinary team (MDT) comprising endocrinologists, neurosurgeons, pathologists, gynaecologists, and radiologists. The patient was diagnosed with a PitNET and functional gonadotroph tumour, and surgical treatment was recommended. And the risks of surgery may include visual field defects, cerebrospinal fluid rhinorrhea, hypopituitarism, and other unexpected events.

On September 6, 2022, endoscopic endonasal transsphenoidal surgery (EETS) was performed to resect the PitNET. The dura mater was cut apart, revealing that the tumour was yellow-brown and solid with clear boundaries. The blood supply of the tumour was normal. The tumour was carefully and slowly resected into small blocks under endoscopy, and the skull base was reconstructed with artificial meninges [Fig. 2(A-C)].

Postoperative pathologic examination confirmed a PitNET. The immunohistochemistry results were as follows: FSH (+), PiT-1 (−), LH (−), growth hormone (−), PRL (−), thyroid-stimulating hormone (−), Ki-67 (1 %), p53 (−).

The postoperative process was smooth, and the patient had no fever, headache, dizziness, cerebrospinal fluid rhinorrhea, no visual field defect, and no vision loss. After surgery, the patient's pituitary gland function was normal , and hormone levels were normal, so there was no hormone replacement therapy. The endocrine examination on the first postoperative day showed that compared with preoperatively, the levels of FSH (3.91 mIU/ml; reference range 3.5–12.5 mIU/ml) and oestradiol (147.8 pg/ml; reference range 12.4–233.0 pg/ml) had significantly decreased to the reference range. Menstruation resumed on the fourth postoperative day, and the patient was discharged on the seventh day. Abdominal ultrasonography on the 10th postoperative day showed that the bilateral ovaries were slightly smaller compared with preoperatively (left ovary: 3.5 × 6.0 cm, right ovary: 3.6 × 6.6 cm). The patient's menstruation returned to normal 1 month after the operation, and endocrine examination results showed that the levels of FSH, LH and oestradiol were normal. Eight months after the operation, skull MRI showed no residual tumour or signs of tumour recurrence [Fig. 3 (A-C)]; abdominal ultrasonography showed that both ovaries were normal.

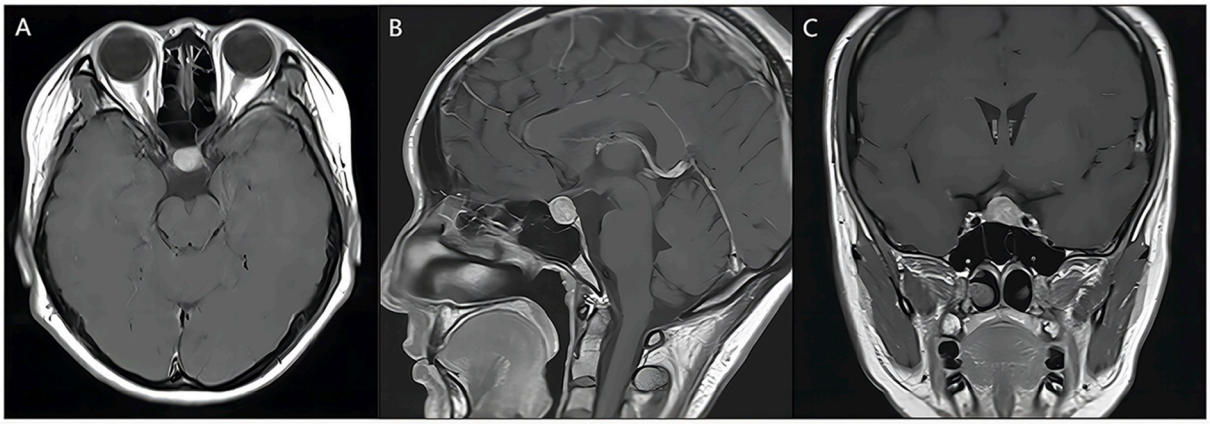

Fig. 1. The preoperative T1-enhanced skull magnetic resonance imaging scan showed a pituitary tumour with uniform enhancement. The presence of pituitary stalk compression was unclear, but the optic chiasm was slightly compressed. The tumour showed a clear boundary with the bilateral cavernous sinuses and no envelopment of the internal carotid artery.

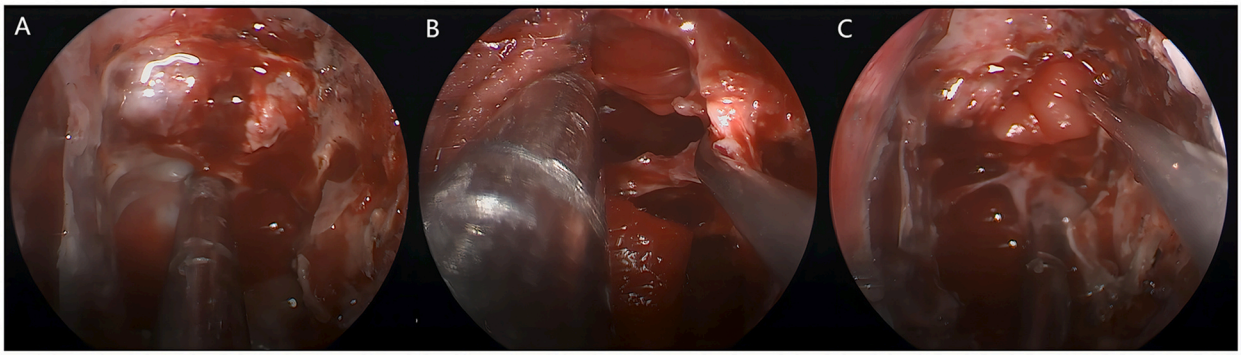

Fig. 2. Surgical resection of the pituitary tumour. Left: Dural incision. Central image: Sella turcica after tumour resection. Right: Reconstruction of the skull base using artificial dura mater.

3. Discussion

PitNETs are classified into functional and nonfunctional PitNETs according to the secretion of hormones. Clinically, approximately 64 % of nonfunctional PitNETs are confirmed to be gonadotroph tumours by immunohistochemical assay [1]. Gonadotroph tumours are usually clinically nonfunctional or asymptomatic, because they do not secrete FSH. However, in rare cases, gonadotroph tumour cells secrete large amounts of FSH. The elevated serum levels of FSH and oestradiol can cause ovarian hyperstimulation syndrome [2]. The symptoms of ovarian hyperstimulation syndrome are classified as mild, moderate, and severe. Mild manifests as abdominal bloating, mild abdominal pain, mild nausea or vomiting. Moderate manifests as abdominal pain, nausea or vomiting. Severe manifests as mild and moderate clinical feature, clinical ascites or hydrothorax, severe dyspnea, anuria or oliguria, weight gain. In some cases severe ovarian hyperstimulation syndrome manifests as abdominal pain or ovarian cyst torsion, which often requires emergency ovariocystectomy or even oophorectomy. The patient in the present case had clinical manifestations of oligomenorrhea, menstrual disturbances, secondary amenorrhea, polycystic ovaries, and ovarian enlargement. Although the patient did not have abdominal pain, abdominal distention, it was a mild form of ovarian hyperstimulation syndrome.

An elevated oestrogen level can provide important diagnostic clues in the endocrine examination. Menstrual abnormalities are a common complaint in women of childbearing age. Sex hormone testing reveals an elevated oestrogen level without suppression of the FSH level. Wang et al., analysed the data of 65 premenopausal patients with functional gonadotroph tumours and found that 92 % of patients had an elevated FSH level and 7.7 % had an elevated LH level [3]. In the present case, the patient's oestrogen level was markedly elevated, her FSH and PRL levels were increased, and her LH level was decreased. A possible reason for these abnormalities is that the excessive secretion of FSH by the gonadotroph tumour stimulated the simultaneous development of multiple follicles in the ovaries, resulting in an obvious increase in the oestrogen level. However, as the tumour cells continued to secrete FSH, the inhibitory effect of negative feedback disappeared and the serum FSH level slightly increased. The decreased LH level may have been related to negative feedback inhibition or irregular LH secretion. The elevated PRL level may have been caused by compression of the pituitary stalk or stimulation by the high level of oestrogen.

The postoperative pathological examination confirmed the diagnosis of a functional gonadotroph tumour in this case. In accordance with relevant literature, most patients with functional gonadotroph tumours have larger PitNETs, which usually grow to the suprasellar region and invade the cavernous sinus. Unlike in previously published cases, no evidence of tumour aggressiveness was

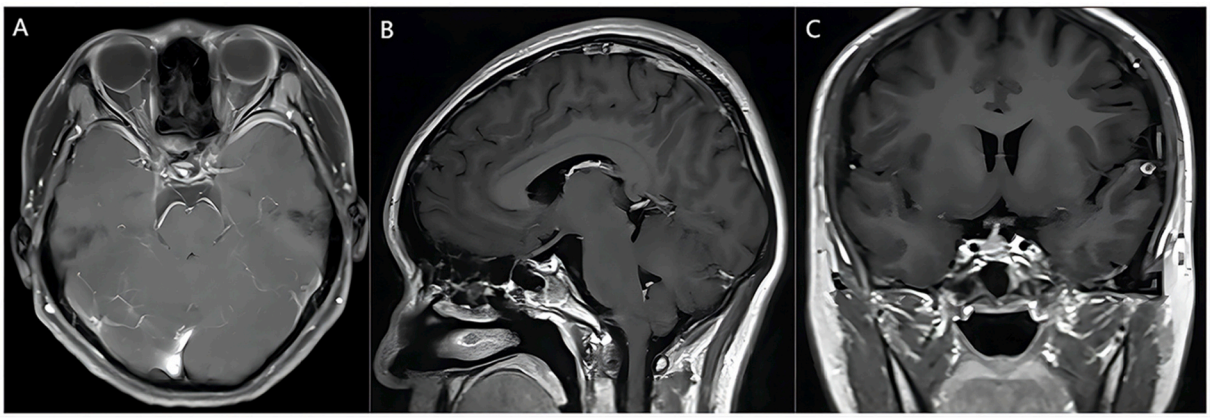

Fig. 3. The 8-month postoperative T1-enhanced skull magnetic resonance imaging scan showed no residual tumour or signs of tumour recurrence.

found in this case. No invasion of the cavernous sinus or sellar diaphragm was found in the preoperative MRI examination or during the operation. The immunohistochemical results showed Ki-67 (1 %) and p53 (−), suggesting that the tumour may have been non-aggressive.

Tumour resection by EETS is the preferred choice for functional gonadotroph tumours because such treatment can normalise endocrine function and resolve symptoms caused by tumour compression and tumour hypersecretion. In premenopausal women, successful surgery can gradually resolve ovarian hyperstimulation syndrome [4]. The tumour in the present case was small, the clinical symptoms of excessive FSH secretion were mild. After tumour resection, the patient's menstrual disturbances immediately improved, the FSF and oestrogen levels significantly decreased to the reference range, the ovaries gradually shrank and returned to normal size, and the polycystic nature of the ovaries disappeared. We believe that young women with PitNETs can be diagnosed with a functional gonadotroph tumour when the FSH and oestrogen levels increase. Small tumours in these patients should be actively treated with surgery. Unnecessary ovarian surgery can be avoided. Our case reports also have certain limitations. The main reason is that the follow-up time is too short, and it is necessary to continue follow-up to monitor the patient's future growth and development and make further evaluation.

4. Conclusion

Functional gonadotroph tumours are rare, and a correct diagnosis is very challenging for gynaecologists and neurosurgeons to achieve. Skull MRI should be performed for young female patients with menstrual disturbances, signs of ovarian stimulation, and elevated levels of FSH and oestradiol. If MRI reveals a pituitary tumour, the diagnosis of functional gonadotroph tumour should be considered. Tumour resection by EETS is the preferred choice for functional gonadotroph tumours. After the operation, the patient should undergo long-term follow-up by pituitary MRI, abdominal ultrasonography, and hormone level measurement.

Declarations

4.1. Data availability statement

The data in the article are available in the article.

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Disclosure of interest

All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

Written informed consent was obtained from the patient for publication of this report. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Informed consent

Informed consent was obtained from the patient described in this report. All data present in the manuscript are anonymised and cannot be associated to the patient.

CRediT authorship contribution statement

Wenzhen Yang: Writing – original draft, Conceptualization. **Jing Zheng:** Writing – original draft. **Hu Yang:** Resources, Investigation. **Qiang Li:** Writing – original draft, Project administration, Conceptualization. **Xiaoqiang Wang:** Writing – review & editing, Funding acquisition. **Yinliang Bai:** Writing – review & editing, Funding acquisition. **Shuting Yang:** Writing – review & editing, Investigation. **Jie Liu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

References

[1] J. Drummond, F. Roncaroli, A.B. Grossman, M. Korbonits, Clinical and pathological aspects of silent pituitary ademomas, J. Clin. Endocrinol. Metab. 104 (7) (2019) 2473–2489, https://doi.org/10.1210/jc.2018-00688.

[2] S. Patel, D. Pacione, I. Fischer, E. Maloku, N. Agrawal, Follicle-stimulating hormone-Producing pituitary adenoma: a case report and review of the literature, AACE Clin Case Rep 5 (3) (2019) e175–e180, https://doi.org/10.4158/ACCR-2018-0454.

[3] L. Wang, H. Liang, C. Deng, Q. Yu, F. Gong, F. Feng, H. You, Z. Liang, B. Chen, K. Deng, J. Ma, R. Wang, Y. Yao, H. Zhu, Functioning gonadotroph adenomas in premenopausal women: clinical and molecular characterization and review of the literature, Pituitary 25 (3) (2022) 454–467, https://doi.org/10.1007/s11102-021-01205-9.

[4] H. Hasegawa, C.L. Nesvick, D. Erickson, S.C. Cohen, Y.U. Yolcu, Z. Khan, A. Raghunathan, T.B. Nippoldt, J.L. Atkinson, J.J.V. Gompel, Gonadotroph pituitary adenoma causing treatable infertility and ovarian hyperstimulation syndrome in female patients: neurosurgical, endocrinologic, gynecologic, and reproductive outcomes, World Neurosurg 150 (2021) e162–e175, https://doi.org/10.1016/j.wneu.2021.02.115.