



Juvenile granulosa cell tumour of the ovary presenting with hyperprolactinaemic amenorrhoea and galactorrhoea

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Summary

Secondary amenorrhoea and galactorrhoea represent a common endocrine presentation. We report a case of an oestrogen-producing juvenile granulosa cell tumour (JGCT) of the ovary in a 16-year-old post-pubertal woman with hyperprolactinaemia amenorrhoea and galactorrhoea which resolved following surgical resection of the tumour. This patient presented with a 9-month history of secondary amenorrhoea and a 2-month history of galactorrhoea. Elevated serum prolactin at 7081 mIU/l and suppressed gonadotropins (LH <0.1 U/l; FSH <0.1 U/l) were detected. Serum oestradiol was significantly elevated at 7442 pmol/l with undetectable β -human chorionic gonadotropin. MRI showed a bulky pituitary with no visible adenoma. MRI of the abdomen showed a 4.8 cm mass arising from the right ovary with no evidence of metastatic disease. Serum inhibin B was elevated at 2735 ng/l. A right salpingo-oophorectomy was performed, and histology confirmed the diagnosis of a JGCT, stage International Federation of Gynaecology and Obstetrics 1A. Immunohistochemical staining for prolactin was negative. Post-operatively, oestrogen and prolactin levels were normalised, and she subsequently had a successful pregnancy. In summary, we present a case of an oestrogen-secreting JGCT with hyperprolactinaemia manifesting clinically with galactorrhoea and secondary amenorrhoea. We postulate that observed hyperprolactinaemia was caused by oestrogenic stimulation of pituitary lactotroph cells, a biochemical state analogous to pregnancy. To the best of our knowledge, this is the first report of hyperprolactinaemia as a result of excessive oestrogen production in the context of a JGCT.

Learning points:

- Hyperprolactinaemia with bilateral galactorrhoea and secondary amenorrhoea has a wide differential diagnosis and is not always caused by a prolactin secreting pituitary adenoma.
- Significantly elevated serum oestradiol levels in the range seen in this case, in the absence of pregnancy, are indicative of an oestrogen-secreting tumour.
- JGCTs are rare hormonally active ovarian neoplasms mostly secreting steroid hormones.
- Serum inhibin can be used as a granulosa cell-specific tumour marker.
- JGCTs have an excellent prognosis in the early stages of the disease.

Background

Hyperprolactinaemia constitutes a common endocrine presentation. The commonest causes of symptomatic non-physiological hyperprolactinaemia are prolactinomas, other pituitary and parasellar tumours, medication use, renal failure and hypothyroidism. Clinically, hyperprolactinaemia typically presents with galactorrhoea, hypogonadism and infertility (1). Treatment depends on the underlying aetiology and may simply involve withdrawal of the causative agent or treatment of the causative endocrine condition. In the case of pituitary or parapituitary lesions, treatment may include a dopamine agonist therapy, surgery or radiotherapy (1).

Ovarian granulosa cell tumours are rare hormonally active neoplasms accounting for ~3–5% of all ovarian cancers (2). Juvenile granulosa cell tumours (JGCTs) of the ovary are considered to be more aggressive than the adult type but also far less common, representing only 5% of all granulosa cell tumours in the paediatric age group (3) (4). Granulosa cell tumours secrete steroid hormones – mostly oestrogens and less commonly androgens and progestins (2), but secretion of prolactin (5) and insulin (6) has been described. Most granulosa cell tumours secrete inhibin which has been used as granulosa cell-specific tumour marker (7). Tumour staging uses the International Federation of Gynaecology and Obstetrics (FIGO) system. Most JGCTs are FIGO stage 1 at the time of diagnosis and have excellent cure rates (5-year survival rate 90–95%) with surgery being the mainstay of therapy. Advanced stages bear a worse prognosis (5-year survival rate 25–50%) and require adjuvant chemotherapy with cisplatin-based regimens (8).

Case presentation

A 16-year-old Eastern European Romani woman (nulligravida and nullipara) presented with a 9-month history of secondary amenorrhoea and a 2-month history of bilateral galactorrhoea. She denied headache or any visual symptoms. Her past medical history was unremarkable with menarche at age 14 and a previously normal menstrual cycle. She was not taking any regular medications apart from paracetamol and ibuprofen over the counter. She had never used hormonal contraception. On examination, visual fields were full on confrontation and cranial nerves were intact. The thyroid was not palpable, and there were no signs of androgen hormone excess. The remainder of the external examination was unremarkable. She was a cigarette smoker (5/day) and denied alcohol consumption and substance misuse.

Investigation

Anterior pituitary function assessment revealed markedly elevated serum prolactin at 7081 mIU/l (reference range 102–496 mIU/l) with negative macroprolactin screen and fully suppressed gonadotropins (luteinising hormone (LH) <0.1 U/l; follicle-stimulating hormone (FSH) <0.1 U/l). Thyrotrophin (TSH) was 3.3 mIU/l (3.9–7.7 mIU/l), free T₄ borderline low at 11.5 pmol/l (12.0–22.0 pmol/l), IGF1 low at 129 µg/l (270–660 µg/l) and adrenocorticotrophin (ACTH) was normal at 21.1 ng/l (reference range at 0900 h <46 ng/l). Serum oestradiol was significantly elevated at 7442 pmol/l with undetectable β-human chorionic gonadotropin (β-hCG). Serum testosterone was borderline elevated at 2.0 nmol/l (0.3–1.7 nmol/l) together with elevated SHBG at >200 nmol/l (32.4–128 nmol/l). Although prolactin levels >5000 mU/l usually indicate the presence of a macroprolactinoma (after exclusion of pregnancy and medication-induced hyperprolactinaemia) (1), MRI of the pituitary with contrast showed an enlarged anterior pituitary with a convex upper border, but no micro or macroadenoma was visible (Fig. 1A).

Given the highly elevated serum oestradiol levels and negative pregnancy test, we considered an ovarian lesion as a source of oestrogens driving lactotroph hyperplasia and prolactin secretion – a state analogous to normal pregnancy. MRI of the abdomen and pelvis showed a 4.8 cm mass within the right ovary and normal appearances of the uterus and left ovary (Fig. 1B). Serum inhibin B levels were elevated at 2735 ng/l (reference range <341 ng/l in premenopausal women) indicating a presence of a granulosa cell tumour of the ovary (7). Other tumour

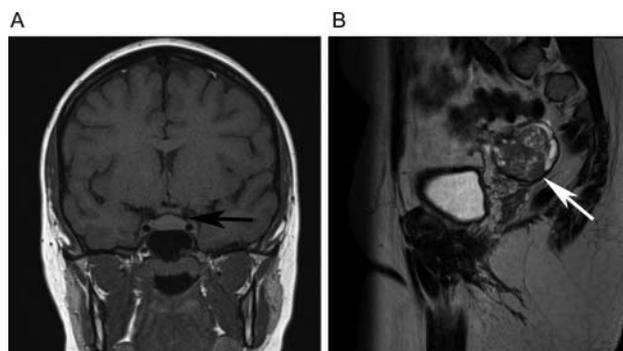


Figure 1
(A) An MRI of the pituitary with contrast, T1-weighted image, coronal view. The pituitary is enlarged and bulges into the suprasellar cistern (black arrow), but there is no evidence of micro or macroadenoma. (B) MRI of the abdomen with contrast (sagittal view) showed a 4.8 cm rounded mass within the right ovary (white arrow) and normal appearances of the uterus and left ovary.

markers including inhibin A (79.7 ng/l; reference range 5–160 ng/l), CA 125 (20 U/ml; reference range 0–30 U/ml) and α -fetoprotein (1.21 μ g/l; reference range <8 μ g/l) were negative.

Treatment

The patient underwent an uneventful right salpingo-oophorectomy, and histology confirmed a JGCT of the right ovary which was staged as FIGO 1A (Fig. 2A). Immunohistochemical analysis of the JGCT specimen was negative for prolactin (Fig. 2B).

Outcome and follow-up

This patient defaulted from endocrine follow-up after surgery. However, she conceived 6 months after the surgery and gave birth to a healthy child. A hormonal profile requested by the patient's general practitioner 2 years after surgery showed a normal oestradiol of 821 pmol/l and normal prolactin of 327 mIU/l. At the time of writing this report, the patient is pregnant with her second child.

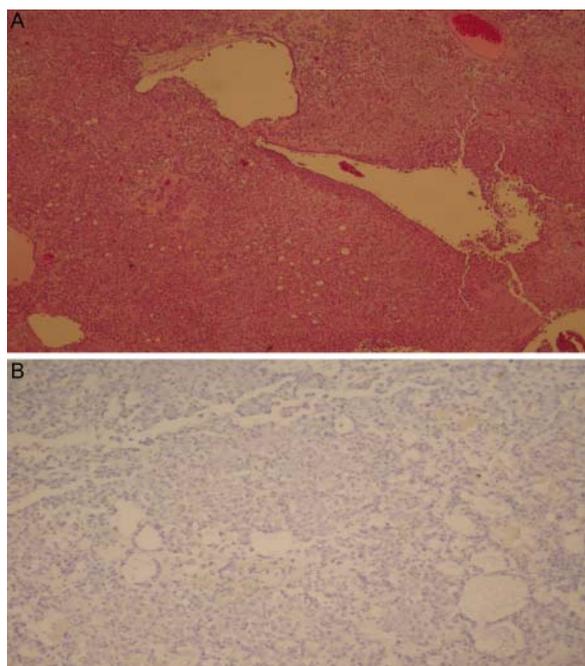


Figure 2
(A) JGCT of the right ovary, FIGO stage 1A. Hematoxylin and eosin staining shows mostly luteinised cells with clear or pale eosinophilic cytoplasm and scattered irregular follicular spaces. (B) Prolactin immunohistochemistry did not identify any significant expression of prolactin within the tumour cells.

Discussion

We present a case of an oestrogen-secreting JGCT in a 16-year-old woman resulting in hyperprolactinaemia and presenting clinically with galactorrhoea and secondary amenorrhoea. This situation, to an extent, resembles normal pregnancy in which prolactin levels increase approximately tenfold (9) and the pituitary increases in volume more than twofold as a result of oestrogenic stimulation of lactotrophs (10). Surgical removal of the ovarian neoplasm resulted in restoration of fertility as evidenced by the patient's pregnancy 6 months after surgery.

An FSH-producing pituitary adenoma presenting with ovarian hyperstimulation syndrome (OHSS), oligomenorrhoea and bilateral galactorrhoea with elevated FSH, oestradiol and prolactin levels has been previously reported (11). Subsequent transsphenoidal surgery of the pituitary macroadenoma resulted in normalisation of hormonal values and resolution of symptoms. Absence of pituitary lesion on MRI and suppressed FSH levels exclude this clinical scenario in the presented case.

To the best of our knowledge, this is the first report of hyperprolactinaemia as a result of excessive oestrogen production in the context of a JGCT. A Finnish group reported of an aggressive JGCT in a 19-year-old woman secreting prolactin but not oestrogen (5) – a scenario which we managed to exclude by the negative immunohistochemical analysis for prolactin in the JGCT specimen. An Italian group reported a JGCT (FIGO stage 1A) in a 16-year-old woman who presented with secondary amenorrhoea (6). Elevated levels of prolactin (approximately twofold of the upper limit of normal) were detected, but oestradiol levels were normal. The JGCT specimen stained negatively for prolactin, and serum prolactin levels did not normalise following the surgery making it difficult to link the mild hyperprolactinaemia to the presence of the tumour.

JGCTs producing oestradiol, 17-hydroxyprogesterone, DHEA and testosterone were reported in two 16-month old girls presenting with several signs of 'precocious puberty' – transient vaginal bleeding, pubic hair, clitoromegaly and breast enlargement which all regressed following surgical removal of the tumour (3). Several cases of JGCTs producing oestradiol were reported in older age groups (4). Of 33 cases of JGCTs, 14 presented with pseudo-precocious puberty and elevated oestradiol levels. In seven of these patients, oestradiol was also measured after surgery and returned to normal levels in all cases (4). However, prolactin and inhibin levels were not measured in any of these patients.

Conclusion

We describe a case of an oestrogen-secreting JGCT with marked hyperprolactinaemia presenting clinically with galactorrhoea and secondary amenorrhoea. Based on immunohistochemistry of the JGCT specimen, we postulate that the observed hyperprolactinaemia was caused by oestrogenic stimulation of pituitary lactotroph cells, a biochemical state analogous to pregnancy. Our case thus illustrates a case of tumour-induced hyperprolactinaemia with a pathophysiology that has not been previously reported in the literature and is currently not reflected in clinical practice guidelines (1).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The authors confirm that written informed consent was obtained from the patient for publication of the submitted article and accompanying images through her signature on the consent form.

Author contribution statement

P Novodvorsky wrote the first draft, did the review of the case and the literature search. A Iqbal, A Lubina-Solomon and J Webster reviewed the patient in the outpatient clinic. Ms F M Kew operated on the patient. All listed authors contributed to the editing process.

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