

Beat the giant: case of a giant prolactinoma during pregnancy on cabergoline

Wael M Almistehi¹ and Mussa H Almalki^{1,2}

¹Obesity, Endocrine, and Metabolism Center, King Fahad Medical City, Riyadh, Saudi Arabia and ²King Fahad Medical City, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Correspondence
should be addressed
to W M Almistehi
Email
wael.almistehi@gmail.com

Summary

Giant prolactinomas are a rare entity; during pregnancy, the risk for complications associated with these tumors is higher. Here, we report a case of a young woman who had an invasive, giant prolactinoma post resection with residual disease who became pregnant. This patient was treated with cabergoline to prevent tumor expansion in pregnancy, resulting in the uneventful delivery of a healthy baby boy.

Learning points:

- Giant prolactinoma can cause both diagnostic and therapeutic challenges given their atypical presentation.
- Accurate diagnosis is paramount to avoid unnecessary surgical intervention or pituitary irradiation.
- This case demonstrates the effectiveness and safety of CAB therapy during pregnancy.

Background

Pituitary tumors account for 10–15% of all intracranial tumors. Prolactinomas are the most frequently occurring pituitary tumors with a prevalence of 3.5–5 per 10 000 inhabitants, according to recent epidemiological studies (1, 2, 3). Prolactinomas are typically microadenomas and they occur more often in women (3), while macroadenomas are usually found in men (4, 5). Giant prolactinomas are a subset of macroadenomas, defined as tumors >4cm in diameter; they are associated with prolactin (PRL) levels >1000ng/mL and typically result in clinical symptoms such as hyperprolactinemia or they present with mass effects (5). Although prolactinomas are benign, giant macroprolactinomas are often locally aggressive, invading surrounding structures (6, 7).

Dopamine agonists (DA) are the first-line treatment for prolactinomas, as these agents can rapidly alleviate neurological symptoms. Further, they are highly effective at normalizing PRL levels, and they induce significant shrinkage of tumor volume in both men and women (8, 9, 10). Surgery is usually reserved for patients who

are intolerant to – or exhibit an inadequate response to – DA; it is also recommended for patients with invasive macroadenomas, as the procedure can be used for tumor debulking and to alleviate neurological deficits (11). Radiotherapy is only used in cases of surgical failure or resistance to DA (12).

During pregnancy, the pituitary gland undergoes lactotroph hyperplasia due to a progressive increase in serum estrogen levels, possibly resulting in a substantial increase in tumor volume (4). The risk of tumor growth is minimal in microadenomas (2.7%), being higher in macroadenomas (15%–35%) (1, 3). It is recommended that patients discontinue DA therapy once pregnancy is confirmed, usually 1–2 weeks after a missed period, limiting potential fetal exposure to only 3–4 weeks (13).

Although prolactinomas are amenable to medical therapy with DA during pregnancy, it is clear that taking bromocriptine and cabergoline (CAB) until conception is safe; however, there is scant evidence to support the idea that continuing the use of bromocriptine or CAB is

safe during pregnancy. The Endocrine Society guidelines recommend discontinuing DAs as soon as pregnancy is confirmed, except for women harboring invasive macroprolactinomas or in patients with evidence of tumor growth and visual and/or headache complaints (14).

Patients should be monitored and evaluated every trimester or more frequently for those with larger tumors, for changes in symptoms such as headaches and visual field defects (14). Here, we describe the case of an invasive, giant prolactinoma, which was misdiagnosed due to a falsely low PRL concentration. In the case described here, the patient became pregnant and was successfully treated with CAB throughout her pregnancy.

Case report

A 29-year-old Saudi female – married, and a mother of two children – presented with nasal obstruction, secondary amenorrhea, and visual disturbance. She initially saw her ear, nose and throat surgeon and her initial investigations revealed an elevated PRL level of 142.5 ng/mL (normal range: 4.15–23.2 ng/mL) using the Cobas assay by Roche (Hoffman-La Roche, Basel, Switzerland). MRI showed a sellar mass measuring 6.2 × 4.22 cm, invading the cavernous sinuses and skull base bones and extending to the nasal cavity, paranasal sinuses and pterygopalatine fosse (Fig. 1A and B), increasing the possibility of the presence of a non-functioning pituitary adenoma. Her visual field examination was normal. She underwent transsphenoidal surgery in November 2013.

The postoperative period was uneventful without any complications. Imaging by CT scans of the brain and MRI scans of the pituitary post-surgery showed a residual pituitary tumor, with removal of 60% of the para-sellar lesion (Fig. 1C and D). The other relevant pituitary hormones were very much within the normal limits, apart from hypothyroidism. The patient was prescribed levothyroxine (75 mg daily) and discharged home in good condition.

The resected tumor tissue showed strong and positive immunostaining for PRL, but it was negative for the other pituitary hormones. After consultation with the endocrinologist, her PRL levels with dilution revealed an increased PRL concentration (3380.95 ng/mL), confirming the diagnosis of an invasive giant prolactinoma.

After surgery, given her positive immunostaining for PRL and high PRL levels after dilution, as well as the presence of gross tumor remnants, treatment was attempted with cabergoline (CAB) at a dose of 0.25 mg twice a week, which improved, stabilized and controlled

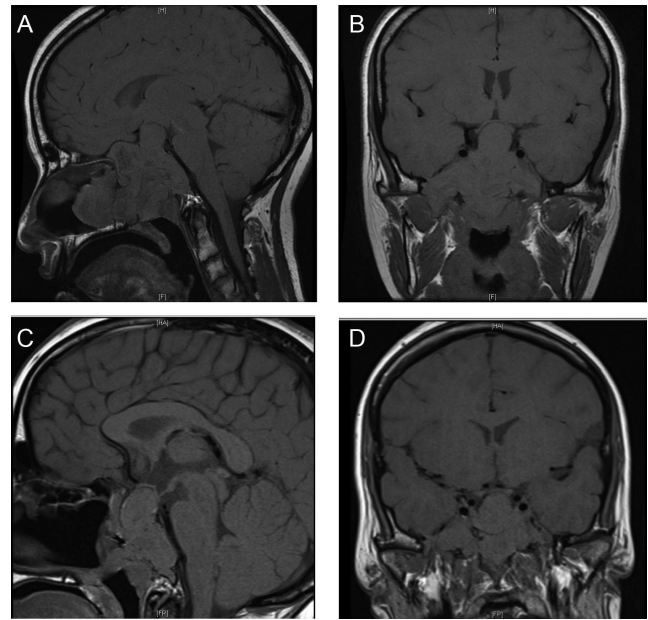


Figure 1

(A and B) Preoperative MRI scan of the pituitary showing a large sellar/suprasellar mass, which invaded the bilateral cavernous sinuses and skull base bones and extended to the nasal cavity, paranasal sinuses and pterygopalatine fosse. (C and D) Postoperative MRI scan of the pituitary showing a residual lesion that appeared to be stable in size and signal intensity at the sellar and suprasellar component, invading the skull base and extending to the nasopharynx. The optic chiasm and optic nerves appear unremarkable; the bilateral internal carotid arteries are again noted to be encircled by the tumor and are still patent.

the disease based on biochemical and radiological findings, and the patient achieved regular menses. The patient asked about the possibility of pregnancy and had been advised to avoid pregnancy due to the substantial risk of tumor growth during pregnancy. The patient's medication was maintained at the same dose, as she showed good biochemical and radiological response to CAB.

In 2016, the patient attended our clinic reporting a 6-week pregnancy that she wanted to continue. Given the tumor characteristics, she was advised to continue CAB at a dose of 0.25 mg twice weekly, followed by monthly clinical visits; monitoring appointments of her high-risk pregnancy was scheduled.

Given the potential risk of tumor enlargement, an MRI pituitary was performed without gadolinium at 26 weeks of gestation which showed a slight increase in adenoma size (Fig. 2A and B), but no headaches or visual disturbances were reported. Ophthalmological and visual field examinations were completely normal. The patient was advised to increase the CAB dose to 0.5 mg twice per week to ensure a further reduction in tumor size, but she declined to do so.

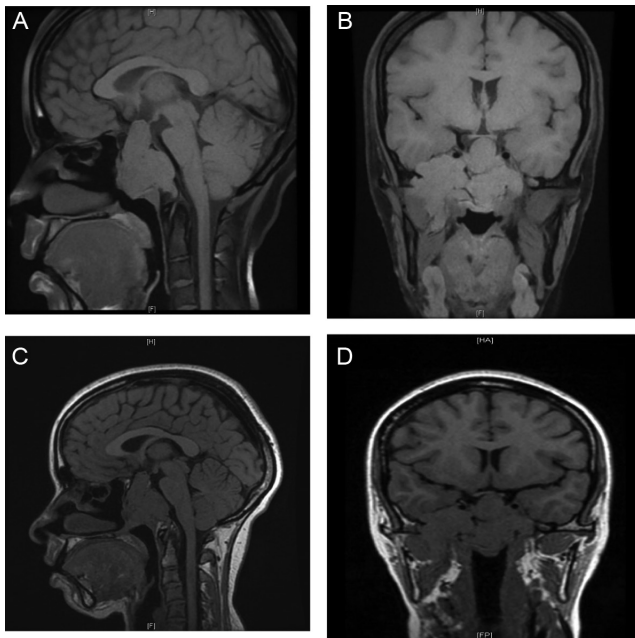


Figure 2
(A and B) Intrapartum (26 weeks' gestation) MRI scan of the pituitary showing a minimal increase in the size of the macroadenoma in the anterior–posterior dimension. The supratentorial component of the tumor just reaches the margin of the optic chiasm. The optic chiasm is thin and moderately atrophied with a mild T2 hyperintense signal abnormality, unchanged as compared with prior studies. (C and D) Postpartum MRI scan of the pituitary showed interval tumor progression since the previous MRI scan. The tumor currently shows more progression extracranially, affecting the intratemporal region and eroding the floor of the right-middle cranial fossa. It subsequently developed into a dural-based enhancing lesion that was noted in continuity with the previous tumor, causing compression and displacement to the right temporal pole. Furthermore, interval progression was noted in the size of the tumor at the roof of the nasopharynx.

The patient remained symptom-free during gestation; she had normal perimetry tests every 3 months until she vaginally delivered a normal, full-term, healthy baby boy. The baby weighed 2.3 kg, and the baby had normal postnatal development.

The postpartum period was uneventful, and CAB was continued at a dose of 0.25 mg twice per week. The patient's PRL levels, as illustrated in Table 1, remained within the normal range (16.6 ng/mL), and an MRI scan showed tumor enlargement (Fig. 2C and D), although the patient reported no symptoms. To decrease the morbidity associated with tumor growth, the CAB dose was increased to 0.5 mg twice per week.

Discussion

This case demonstrates some of the diagnostic difficulties associated with skull base tumors. Here, we reported a

Table 1 Prolactin levels and MRI findings during follow-up from diagnosis until postpartum.

| Time of measurement | Prolactin levels (ng/mL) (with dilution) | MRI pituitary lesion size (cm) |
|-------------------------|--|--------------------------------|
| Preoperative (baseline) | 142.5 ng/mL* | |
| With dilution | 3380.95 | 6.2 × 4.22 |
| Postoperative | 15.3 | 4.7 × 2.9 |
| Intrapartum | 18.0 | 4.9 × 3.4 |
| Postpartum | 16.6 | 5.0 × 3.7 |

*Initial measurement, without dilution.

patient with an unusual clinical presentation, in which the diagnosis of an invasive, giant macroprolactinoma was only made following surgical debulking and the discovery of an elevated PRL level after retesting of the serum prolactin sample with serial dilutions. To the best of our knowledge, this is the second case of an invasive, giant macroprolactinoma during pregnancy. In contrast to the first case that was diagnosed during pregnancy and managed with bromocriptine, our patient was diagnosed before conception and was managed with CAB during the entire course of her pregnancy. PRL-secreting adenomas are the most common pituitary tumors in women of childbearing age (3). Prolactinomas are classified based on their size as macroadenomas (>1 cm) or microadenomas (<1 cm) (4, 5). Approximately 90% of pituitary tumors are intrasellar adenomas, while the remainder are macroadenomas. Giant prolactinomas (>4 cm) are a rare pituitary tumor subtype associated with high serum PRL levels that are >1000 ng/mL (5). The correct diagnosis of this subtype is critical, as surgical resection is associated with significant morbidity and mortality (15, 16); treatment with DA can effectively lower serum PRL levels and significantly reduce tumor size in most cases (17).

Pituitary adenomas are diverse, even in the case of symptomatic hyperprolactinemia. Although non-functioning adenomas can exhibit stalk effects and PRL levels can reach up to 200 ng/mL, diagnostic challenges remain a primary concern in such scenarios (18, 19). The presence of a high-dose hook effect, which occurs when there is a lack of enough antibodies to bind to each end of all antigenic PRL peptides, can further complicate diagnosis. Given that extreme levels of PRL are present in the case of giant macroprolactinomas, most of PRL will form a single antibody; therefore, only a few PRL peptides will be detected using the most commonly used assays, resulting in falsely low serum PRL levels and subsequent misdiagnosis, ultimately leading to unnecessary pituitary surgery with serious morbidities. Presence of the hook



effect can be avoided in monoclonal sandwich assays using two-step processing or by serial dilution in one-step processing (20, 21).

CAB is the first-line treatment for giant macroprolactinomas; extensive evidence has shown the effectiveness and safety of CAB. This DA can normalize PRL levels by around 69–75%, and it can also achieve a 98% decrease in PRL levels at doses of 3.5 mg per week. CAB can further reduce tumor sizes anywhere from 26 to 90% (22).

Once pregnancy occurs in women with prolactinomas, there are two main concerns during pregnancy; first, there is the increase in tumor size during pregnancy that results from increased estrogen levels, which induces lactotroph cell hyperplasia (23). Women with microadenomas have a <3% chance of symptomatic tumor growth during pregnancy as compared to a 25–30% chance of tumor growth in women with recently diagnosed macroadenomas and/or without previous long-term treatment (23, 24). Second, there is the effect of DA on early fetal development and pregnancy outcomes. The data available on the use of bromocriptine in more than 6000 pregnancies (studied at the time of conception or during pregnancy) indicated no increased risk of spontaneous abortions, congenital malformations or neonatal abnormalities (25, 26). Similarly, CAB studies showed no significant difference in the incidence of spontaneous abortions, ectopic pregnancies or neonatal malformations when compared to the general population (27, 28).

The latest guidelines recommend discontinuing DA in women with microadenomas as soon as pregnancy is confirmed, as excellent outcomes can be achieved with close clinical monitoring. Conversely, women with large macroadenomas and those with extrasellar extensions need to continue DA therapy throughout the pregnancy, as the risk of tumor enlargement is relatively high (14). CAB is more efficacious and presents with better tolerability when it is used to reduce PRL levels and control tumor size when compared with bromocriptine; however, no studies have examined these outcomes during pregnancy as yet. In the case presented here, once pregnancy was confirmed, and considering the risk of tumor enlargement and the potential need for surgery, it was decided to continue lower-dose CAB treatment during pregnancy. The choice to continue CAB was very effective, as it facilitated the course of the pregnancy, maintained the tumor size in this patient and was associated with favorable neonatal outcomes.

To date, publications on the use of CAB during pregnancy have been limited. There are only 16 cases

of pregnant women treated with CAB during the entire pregnancy, including our patient; in all cases, no abnormalities were noted in the infants, except one case had an intrauterine death at 34 weeks when the mother had severe preeclampsia (29).

Serial PRL measurements during pregnancy are not necessary due to the high variability of PRL concentrations during pregnancy (4). In this patient, given the initial tumor characteristics, PRL measurements were carried out throughout the pregnancy and always remained within the normal range.

MRI examinations during pregnancy are not required; however, they can be performed without gadolinium, as there is no evidence of harm to the fetus from either MRI scans or gadolinium (9). In this patient, and given the potential risk of tumor enlargement, an MRI scan of the pituitary was performed in the second trimester without gadolinium; it showed a mild increase in the size of the adenoma when compared with the previous MRI. Moreover, there are no data to suggest that breastfeeding is associated with a significant increase in serum PRL levels or in the risk of tumor growth (27, 30). Thus, women can breastfeed normally, but the patient in our case was not able to lactate as she was on DA.

Pregnancy can induce remission of hyperprolactinemia, and macroprolactinomas can occur in 64–70% of cases (31, 30). The mechanism underlying this phenomenon is unclear, but it may be attributed to the auto-infarction of the tumor (32). In our patient, the last MRI scan that was performed 2 months after delivery showed moderate progression, primarily noted in the right-middle cranial fossa and at the roof of the nasopharynx (Fig. 2C and D). Data on postpartum remission rates for these tumors are very limited. Some studies reported significant reductions in PRL levels and tumor volume postpartum when compared with values obtained before pregnancy (31, 33). The impact of pregnancy on giant prolactinomas has not yet been reported. Interestingly, in our patient, treatment with CAB had to continue, as the patient did not demonstrate tumor shrinkage after pregnancy. Furthermore, if the patient continues to experience further tumor expansion despite DA therapy, the clinical team may need to consider medical therapy with temozolomide, radiotherapy or surgical debulking.

Conclusion

Pregnancy in a patient with an invasive, giant macroprolactinoma is rare and its treatment is challenging. This case demonstrates the effectiveness



and safety of CAB therapy during pregnancy. Although the patient's adenoma size increased slightly during pregnancy, she had a successful pregnancy with favorable fetal outcomes. Our case further supports the importance of making an accurate diagnosis and initiating proper treatment before pregnancy. Also, a multidisciplinary team involving endocrinologists, neurosurgeons and obstetricians is required for safe outcomes for both the mother and newborn.

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

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

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