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Approach to the management of rare clinical presentations of macroprolactinomas in reproductive-aged women

Ana Espinosa De Ycaza [a,*], Alice Y. Chang [b], Jani R. Jensen [c], Zaraq Khan [d], Dana Erickson [e]

[a] Division of Endocrinology, Diabetes, Metabolism, and Nutrition, 200 First Street SW, Mayo Clinic, Rochester, MN, 55905, United States
[b] Division of Endocrinology, Diabetes, Metabolism, and Nutrition, 200 First Street SW, Mayo Clinic, Rochester, MN, 55905 United States
[c] Division of Reproductive Endocrinology and Infertility, 200 First Street SW, Mayo Clinic, Rochester, MN, 55905, United States
[d] Division of Reproductive Endocrinology and Infertility, 200 First Street SW, Mayo Clinic, Rochester, MN, 55905, United States
[e] Division of Endocrinology, Diabetes, Metabolism, and Nutrition, 200 First Street SW, Mayo Clinic, Rochester, MN, 55905, United States

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ABSTRACT

Objective: To describe 2 cases of macroprolactinomas with atypical presentation in women desiring pregnancy that illustrate important considerations in the management approach for macroprolactinomas in reproductive-aged women.

Patient(s): Case 1 was a 26-year-old woman referred to our institution for possible tumor resection after pituitary apoplexy during her first pregnancy. Instead, she underwent treatment with cabergoline for a year with goals of normalization of prolactin and decrease in tumor size to <1 cm before trying to conceive. Case 2 was an 18-year-old woman with a macroprolactinoma intolerant to dopamine agonists. She underwent stereotactic radiosurgery, with marked reduction in tumor size and normalization of prolactin levels. She conceived and delivered a healthy infant 3 years after radiosurgery.

Conclusion: Management of macroprolactinomas in women desiring pregnancy requires careful consideration of alternatives to surgery which could impair pituitary function and fertility and awareness of treatment goals that can minimize the risks for pituitary apoplexy and vision loss during pregnancy. It is important to increase awareness of these options prior to initiation of treatment and conception.

1. Introduction

Hyperprolactinemia due to prolactinoma is an important and treatable cause of infertility in women [1]. Most prolactinomas are microadenomas (lesions <1 cm) and may be associated with galactorrhea, amenorrhea, and infertility. In contrast, macroprolactinomas (lesions ≥1 cm) have the potential of causing progressive mass effects, including visual field defects, headaches, or development of hypopituitarism. When considering treatment of macroprolactinomas in reproductive-age women, clinicians must not only consider restoration of fertility, they must also be aware of potential complications during pregnancy, including vision loss, pituitary apoplexy, and effects of therapy on the fetus. These considerations highlight the need to be vigilant about the duration of medical therapy and treatment goals prior to trying to conceive and communicate the importance of these decisions to the patient and care providers to minimize the risk for complications during pregnancy. For women intolerant or resistant to medications, alternatives to surgical resection of macroadenomas must be carefully considered because of the risk for impaired pituitary function after surgery.

We report 2 challenging cases of macroprolactinomas in reproductive-aged women to illustrate the decision-making process. We also include a review of the relevant literature describing management approaches.

2. Cases

2.1. Case 1

A 26-year old G0 woman with a history of a macroprolactinoma was referred for possible surgical resection of the tumor. She reported eight years of oligomenorrhea, with six to nine menstrual cycles per year. At age 23, she was found to have a prolactin level of 14,869 pmol/l (normal: 130–1174 pmol/l) during a work-up for infertility. Pituitary magnetic resonance imaging (MRI) revealed a 1.9 cm × 1.3 cm pituitary mass consistent with an adenoma. Thyroid function tests, serum cortisol and IGF-1 levels were normal. The patient was initiated on oral contraceptives and bromocriptine (2.5 mg, twice daily) which decreased her

Abbreviations: MRI, magnetic resonance imaging; DA, dopamine agonists; IGF-1, Insulin-like growth factor-1.

* Corresponding author.
E-mail addresses: espinosadeycaza.ana@mayo.edu (A. Espinosa De Ycaza), chang.alice1@mayo.edu (A.Y. Chang), jensen.jani@mayo.edu (J.R. Jensen), khan.zaraq@mayo.edu (Z. Khan), erickson.dana@mayo.edu (D. Erickson).

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prolactin to 1304 pmol/l. Repeat imaging was obtained which demonstrated no change in tumor size at 6 months. Because symptoms of nausea and dizziness limited her compliance with bromocriptine, she was switched to cabergoline (0.25 mg, twice weekly). After three months of cabergoline, prolactin decreased further to 174 pmol/l and the tumor decreased slightly in size to 1.9 cm × 0.8 cm. The patient missed one refill of oral contraceptives and became pregnant 1 month later. Dopamine agonist (DA) therapy was discontinued when the pregnancy was confirmed.

During the third trimester, at 28 weeks gestation, the patient presented with an acute onset of severe headache. MRI showed apoplexy into the tumor, which increased in size to 1.4 × 2.0 × 1.2 cm, with evidence of right cavernous sinus invasion (Fig. 1A–C). Visual field testing was normal. She started glucocorticoid replacement therapy because of low random cortisol levels (96.6 nmol/l) and concern for secondary adrenal insufficiency. Cabergoline was reinitiated at 0.25 mg twice weekly. The remainder of her pregnancy was uneventful; she delivered a full-term, 3.1-kg healthy baby via vaginal delivery with vacuum assistance.

Postpartum, DA therapy was changed back to bromocriptine and oral contraceptives were restarted. One week after delivery, the tumor had slightly increased to 1.4 × 2.4 × 1.4 cm. After 6 months of bromocriptine, her prolactin level was 1304 pmol/l and repeat imaging showed a decrease in size (1.1 × 1.4 × 1.0 cm) with persistent right cavernous sinus invasion. Repeat imaging another 6 months later showed no change in size. She was able to taper off hydrocortisone within a year of delivery.

With no significant change in size of the tumor on DA therapy, she was referred to our institution for consideration of surgery to reduce the risk of pituitary apoplexy in a subsequent desired pregnancy. With the cavernous sinus invasion decreasing the chance for surgical cure and considering the risks of pituitary injury and impaired fertility, we recommended that she switch to cabergoline therapy for a year with the goal of stabilizing the adenoma and reducing its size to <1 cm before trying to conceive again. With cabergoline, her prolactin decreased further to 478 pmol/l. After additional 10 months of cabergoline therapy, MRI showed the tumor had decreased to <1 cm, and her prolactin remained at 522 pmol/l. She discontinued oral contraceptives and became pregnant 4 months later. Her pregnancy has been uneventful through the third trimester of pregnancy. Prolactin levels were not closely monitored during her second pregnancy as they are not reliable throughout gestation. The levels can significantly increase with pregnancy per se.

2.2. Case 2

An 18-year-old G0 woman presented with a 4-year history of galactorrhea and an 8-month history of secondary amenorrhea. Her prolactin level was 7174 pmol/l (reference, 130–1174 pmol/l). Thyroid function tests, serum cortisol and IGF-1 levels were normal. A brain MRI showed a normal-appearing sella with an asymmetric, hypoenhancing 1.1 cm soft-tissue mass in the left cavernous sinus, consistent with a pituitary adenoma (Fig. 1D–E). Medical therapy was attempted with both bromocriptine and subsequently cabergoline but the patient developed nausea and severe fatigue with both medications. She also reported side effects to oral contraceptive pills. Given her symptoms, intolerance to dopamine agonists, and tumor location in the cavernous sinus, gamma knife radiosurgery was recommended. She underwent stereotactic radiosurgery with 50 Gy as the maximal dose and 25 Gy administered to the margins of the tumor without complications. A repeat MRI 1 year after radiosurgery showed significant involution of the mass in the left cavernous sinus. Her prolactin levels over the 2-year period after radiosurgery progressively decreased from 7174 to 1304 pmol/l. Pituitary function remained intact. The galactorrhea resolved, menstrual periods resumed, and she was able to spontaneously conceive 3 years after radiosurgery; she delivered a full-term, 3.5-kg healthy baby via vaginal delivery. Six years after radiosurgery, her prolactin levels continue to be normal (435 pmol/l), with normal pituitary function, and the child has normal development.

3. Discussion

These cases illustrate the decision-making process involved when considering therapeutic options for macroprolactinomas before, during,

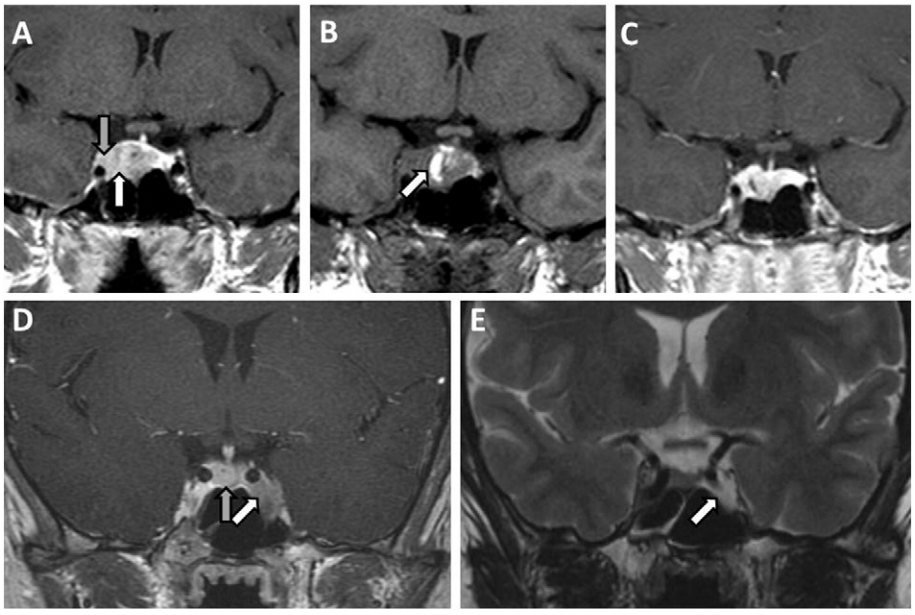

Fig. 1. Magnetic resonance images. Figure parts A–C correspond to Case 1; parts D–E correspond to Case 2. A, T1 coronal image with gadolinium shows a pituitary macroadenoma with right cavernous sinus invasion (white arrow indicates pituitary tumor, gray arrow indicates right cavernous sinus invasion). B, T1 coronal image without gadolinium during pregnancy shows apoplexy (white arrow indicates intratumoral hemorrhage). C, T1 coronal image with gadolinium shows reduced tumor size after dopamine agonist therapy 6 months after her first pregnancy with persistent right cavernous sinus invasion. D, T1 coronal image with gadolinium shows an asymmetric soft-tissue area in the left cavernous sinus (white arrow), which corresponded to a 1.1-cm macroprolactinoma (gray arrow indicates normal pituitary tissue). E, fast spin-echo image 4 years after radiosurgery shows tumor involution in the left cavernous sinus (white arrow).