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Rapid Re-expansion of a Macroprolactinoma After Early Discontinuation of Bromocriptine

John J. Orrego, William F. Chandler, and Ariel L. Barkan

Pituitary and Neuroendocrine Center, Section of Neurosurgery, Department of Surgery (WFC, ALB) and Division of Endocrinology and Metabolism, Department of Internal Medicine (JJO, ALB), University of Michigan Medical Center, Ann Arbor, Michigan

Abstract. **Prolactin (PRL)-secreting pituitary adenomas are the most common functioning pituitary tumors. Medical treatment with dopamine agonists is the therapy of choice for macroprolactinomas (≥10 mm). Withdrawal of bromocriptine after weeks or months of uninterrupted therapy has been associated with rapid tumor re-expansion as evidenced by x-ray and CT scanning of the pituitary region. We report a patient with a giant macroprolactinoma who had a dramatic response to bromocriptine (tumor volume shrinkage of 53% within a month) but rapid re-expansion to its original dimensions one week after discontinuation of bromocriptine. To our knowledge, this is the first time that the rapid shrinkage/re-expansion of a macroprolactinoma has been documented with serial MRI scans.**

Keywords. **hyperprolactinemia, prolactinoma, bromocriptine, pituitary tumors, dopamine agonists**

Introduction

Prolactin (PRL)-secreting pituitary adenomas account for 60% of all functioning-pituitary tumors. Men and postmenopausal women who harbor macroprolactinomas (≥10 mm) frequently come to medical attention with symptoms of mass effect such as visual disturbance or hypopituitarism. Irrespective of the size, these tumors are treated medically with dopamine agonists [1]. Transsphenoidal surgery [2] and radiotherapy [3] are secondary options reserved for the patients who are resistant to dopamine agonists or who do not tolerate them. Bromocriptine and cabergoline are the only two dopamine agonists approved in the United States for the treatment of prolactinomas [4], although pergolide is a very effective alternative for men and postmenopausal women [5]. These medications should probably be taken indefinitely to maintain clinical, hormonal and radiological control of the tumor [6]. Although withdrawal of bromocriptine has been previously shown to cause tumor re-expansion [7], documentation of significant initial tumor shrinkage, re-enlargement after bromocriptine discontinuation, and subsequent contraction after bromocriptine reinstitution has not been investigated with newer imaging techniques. We report a patient with dramatic increase in tumor volume to its original size after early bromocriptine discontinuation as evaluated with serial MRI scans.

Case Report

A 26-yr-old man with new onset throbbing headaches presented to the emergency room on July 7, 1999 complaining of loss of vision in the left eye. He immediately underwent a pituitary MRI that revealed a giant pituitary tumor (vertical diameter 5.5 cm, lateral diameter 5.5 cm, and anteroposterior diameter 5.2 cm) with suprasellar extension and compression of the optic chiasm (Fig. 1a). Serum PRL level was markedly elevated at 18,494 ng/ml, testosterone was low at 1.1 ng/ml, and random cortisol was normal at 18 ug/dl. Formal visual testing was not performed at that time. He was placed on bromocriptine 2.5 mg twice daily with rapid amelioration of his headaches but persistence of his visual abnormality. However, he experienced significant side effects, including postural dizziness and nausea. One month later (August 7, 1999) a repeat pituitary MRI showed that the tumor volume had decreased by 53% (vertical diameter 3.0 cm, lateral diameter 5.5 cm, and anteroposterior diameter 4.5 cm) and that the pressure on the optic chiasm had been relieved (Fig. 1b). Immediately after that, the patient discontinued the bromocriptine on his own and several days later his headaches recurred. He underwent another MRI one week after discontinuation of bromocriptine. The tumor had re-expanded to its original dimensions (Fig. 1c), and at that time PRL was 5,583 ng/ml. Reinstitution of his previous dose of bromocriptine resulted in rapid disappearance of his headaches but not change in his visual abnormality. Six weeks later he reported increase in libido, improvement in quality of erections and facial

Address for correspondence: Ariel L. Barkan, M.D., 3920 Taubman Center, University of Michigan Medical Center, Ann Arbor, MI, 48109-0354. Tel: (734) 936-5504; Fax (734) 936-9240; E-mail address abarkan@umich.edu

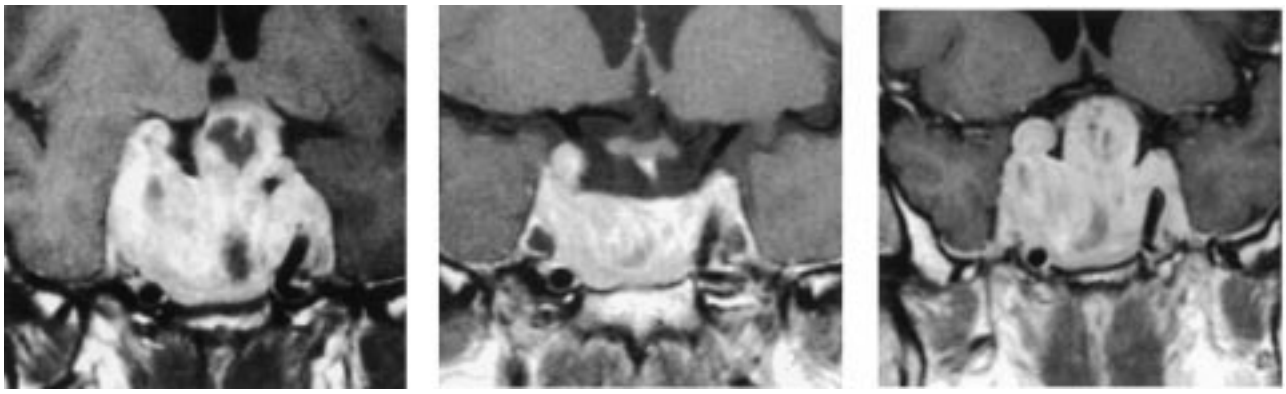

Fig. 1. *Coronal gadolinium-enhanced T1-weighted pituitary magnetic resonance images before (a) and after one month (b) of bromocriptine administration, and one week after bromocriptine discontinuation (c). Fig. 1a shows a 5.5 × 5.5 × 5.2-cm sellar mass with parasellar and suprasellar extension and compression of the optic chiasm. The mass has also cystic components and a small hemorrhagic area. Fig. 1b shows significant volume tumor shrinkage with complete decompression of the optic chiasm. Fig. 1c demonstrates complete re-expansion of the macroprolactinoma with compression of the optic chiasm.*

acne. He had bilateral galactorrhea on expression. Formal visual field study revealed complete left temporal hemianopsia. PRL level decreased significantly to 319 ng/ml, testosterone was low at 0.66 ng/ml, and FT_4 was normal at 1.07 ng/dl. Despite his excellent response to bromocriptine, he was switched to pergolide 0.1 mg twice daily because of side effects with the former. He returned 4 months later for follow up when galactorrhea had disappeared but the left temporal hemianopsia was unchanged. PRL level continued to decline but was still above the normal range at 90.5 ng/ml. Testosterone level was still low at 0.59 ng/ml. A new pituitary MRI at that time showed additional tumor shrinkage (Fig. 2).

Discussion

We have described a young man with a short history of symptoms related to pituitary mass effect due to a macroprolactinoma and his clinical, hormonal, and radiological course after his voluntary discontinuation of bromocriptine. Withdrawal of bromocriptine resulted in re-expansion of the tumor to its original size within a week. Reinstitution of dopamine agonists produced significant tumor shrinkage.

Bromocriptine is a semisynthetic ergot alkaloid that normalized PRL levels in 80–90% and shrinks tumor size in more than 70% of patients with prolactinomas [8]. The time course of tumor shrinkage is variable. Some patients have improvement in visual fields defect within 24 to 72 hours or demonstrate significant reduction in tumor size within a week. Others have more delayed responses, but usually achieve the maximal tumor shrinkage during the first 6 months of therapy. Progressive decrease in adenoma size may continue for over a year [6]. Our patient initially responded extremely well to bromocriptine with 53%-tumor volume shrinkage within a month, but experienced significant side effects with subsequent discontinuation of this medication.

The mechanism of action of bromocriptine in tumor shrinkage and PRL normalization is complex [9]. In vitro studies have shown that bromocriptine reduces PRL and DNA synthesis, PRL mRNA levels, cell multiplication, and tumor growth [10,11] Studies with DNA flow cytometry have shown that low doses of bromocriptine produce increase in the relative number of cells in the S phase but decrease of those in the G1 phase, while higher doses cause inhibition of PRL syn-

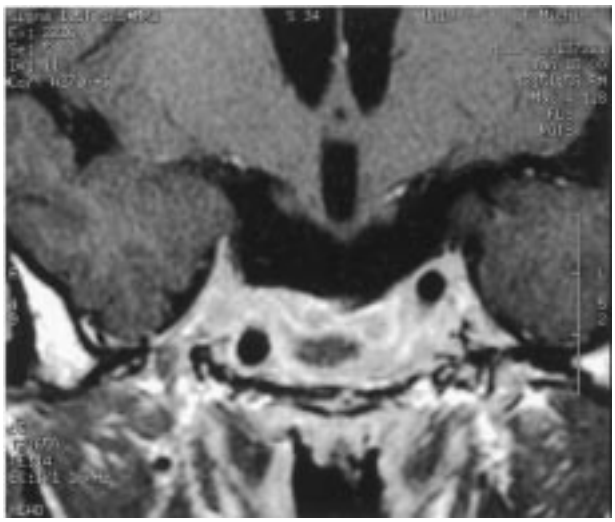

Fig. 2. *Coronal gadolinium-enhanced T1-weighted pituitary magnetic resonance image after 5 months of pergolide therapy. Significant tumor shrinkage is maintained and the optic chiasm is fully decompressed.*

thesis and cell division [12]. Bromocriptine initially reduces the number of exocytosis and PRL secretory granules, suggesting inhibition of PRL release as the rapid mechanism of action [13,14]. However, the most important mechanism of tumor shrinkage is reduction in the size of lactotroph adenomatous cells due to regression of rough endoplasmic reticulum and Golgi apparatus with subsequent cessation of PRL synthesis [11,15–17]. With chronic bromocriptine administration, lactotroph tumorous cells show fragmentation of rough endoplasmic reticula and cytoplasm, macrophage infiltration, aggregation of nuclear chromatin, and deposits of collagen between cells [18,19]. Finally, prolonged administration of bromocriptine may also exert an antimitotic effect on some prolactinomas [20].

Withdrawal of bromocriptine or other dopamine agonists in the setting of a macroprolactinoma is usually followed by PRL increase and/or tumor enlargement. In three patients with macroprolactinomas who had significant tumor shrinkage, bromocriptine was held with subsequent PRL elevation and tumor growth as soon as 5 days later as evidenced by CT scanning [16]. Withdrawal of bromocriptine for 6 days after one year of uninterrupted therapy in a woman with a macroprolactinoma was followed by PRL increase and tumor re-expansion by CT scanning [21]. Another patient with a large prolactinoma who presented with bilateral temporal hemianopsia was placed on bromocriptine with complete resolution of visual abnormalities and PRL normalization. A repeat CT scan a year later showed a partially empty sella. Within 2 weeks of bromocriptine discontinuation, tumor re-expanded and bitemporal hemianopsia recurred [7]. Longer therapy with dopamine agonists may also be accompanied by PRL elevation after withdrawal, although not always by tumor enlargement. After 1.5 to 7 years on bromocriptine or pergolide, 14/15 patients had increase in PRL levels after stopping these medications, but only 1/15 had tumor enlargement after a 5 to 39-week follow up [22]. Similarly, discontinuation of bromocriptine after 3.5 to 7 years of therapy, led to PRL elevation in 11/12 patients with macroprolactinomas but tumor re-expansion in only 1/12 [23]. Wang et al. reported a patient with a macroprolactinoma who was on bromocriptine for 10 years and the PRL was normal and tumor stable two years after drug withdrawal [24]. In the long-term, dopamine agonists can be reduced to their lowest effective dose that maintains PRL level within the normal range [25]. Our patient had a dramatic tumor enlargement after discontinuation of bromocriptine for one week. To our knowledge, this is the first demonstration of rapid PRL-secreting pituitary tumor re-expansion after bromocriptine discontinuation documented by MRI scanning.

We conclude that patients with macroprolactinomas who have responded to dopamine agonists should be warned about the possibility of rapid tumor re-expansion after their discontinuation, particularly within the first year of treatment.

References

1. Molitch ME, Thorner MO, Wilson C. Management of prolactinomas. *J Clin Endocrinol Metab* 1997;82:996–1000.
2. Soule SG, Farhi J, Conway GS, Jacobs HS, Powell M. The outcome of hypophysectomy for prolactinomas in the era of dopamine agonist therapy [see comments]. *Clin Endocrinol (Oxf)* 1996;44:711–716.
3. Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Role of radiation therapy in clinical hormonally-active pituitary adenomas. *Radiother Oncol* 1996;41:45–53.
4. Orrego JJ, Barkan AL. Pituitary disorders. Drug treatment options. *Drugs* 2000▽:93–106.
5. Freda PU, Andreadis CI, Khandji AG, Khoury M, Bruce JN, Jacobs TP, Wardlaw SL. Long-term treatment of prolactin-secreting macroadenomas with pergolide. *J Clin Endocrinol Metab* 2000;85:8–13.
6. Molitch ME. Medical treatment of prolactinomas. *Endocrinol Metab Clin North Am* 1999;28:143–169.
7. Thorner MO, Perryman RL, Rogol AD, Conway BP, Macleod RM, Login IS, Morris JL. Rapid changes of prolactinoma volume after withdrawal and reinstitution of bromocriptine. *J Clin Endocrinol Metab* 1981;53:480–483.
8. Molitch ME. Pathologic hyperprolactinemia. *Endocrinol Metab Clin North Am* 1992;21:877–901.
9. Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* 1992;13:220–240.
10. MacLeod RM, Lehmeyer JE. Suppression of pituitary tumor growth and function by ergot alkaloids. *Cancer Res* 1973;33:849–855.
11. Maurer RA. Dopaminergic inhibition of prolactin synthesis and prolactin messenger RNA accumulation in cultured pituitary cells. *J Biol Chem* 1980;255:8092–8097.
12. Johansen PW, Clausen OP, Haug E, Fossum S, Gautvik KM. Effects of bromocriptine on cell cycle distribution and cell morphology in cultured rat pituitary adenoma cells. *Acta Endocrinol (Copenh)* 1985;110:319–328.
13. Niwa J, Minase T, Mori M, Hashi K. Immunohistochemical, electron microscopic, and morphometric studies of human prolactinomas after short-term bromocriptine treatment. *Surg Neurol* 1987;28:339–344.
14. Hassoun J, Jaquet P, Devictor B, Andonian C, Grisoli F, Gunz G, Toga M. Bromocriptine effects on cultured human prolactin-producing pituitary adenomas: in vitro ultrastructural, morphometric, and immunoelectron microscopic studies. *J Clin Endocrinol Metab* 1985;61:686–692.
15. Mori H, Mori S, Saitoh Y, Arita N, Aono T, Uozumi T, Mogami H, Matsumoto K. Effects of bromocriptine on prolactin-secreting pituitary adenomas. Mechanism of reduction in tumor size evaluated by light and electron microscopic, immunohistochemical, and morphometric analysis. *Cancer* 1985;56:230–238.
16. Nissim M, Ambrosi B, Bernasconi V, Giannattasio G, Giovanelli MA, Bassetti M, Vaccari U, Moriondo P, Spada A, Travaglini P, Faglia G. Bromocriptine treatment of macroprolactinomas: studies on the time course of tumor shrinkage and morphology. *J Endocrinol Invest* 1982;5:409–415.
17. Barrow DL, Tindall GT, Kovacs K, Thorner MO, Horvath E, Hoffman JC Jr. Clinical and pathological effects of bro-

mocriptine on prolactin-secreting and other pituitary tumors. *J Neurosurg* 1984;60:1–7.
18. Kovacs K, Stefaneanu L, Horvath E, Lloyd RV, Lancranjan I, Buchfelder M, Fahlbusch R. Effect of dopamine agonist medication on prolactin producing pituitary adenomas. A morphological study including immunocytochemistry, electron microscopy and in situ hybridization. *Virchows Archiv A Pathol Anat Histopathol* 1991;418:439–446.
19. Anniko M, Wersall J. Clinical and morphological findings in two cases of bromocriptine-treated prolactinomas. *Acta Pathol Microbiol Scand [A]* 1981;89:41–47.
20. Gen M, Uozumi T, Ohta M, Ito A, Kajiwara H, Mori S. Necrotic changes in prolactinomas after long term administration of bromocriptine. *J Clin Endocrinol Metab* 1984;59:463–470.
21. Vance ML, Evans WS, Thorner MO. Drugs five years later. Bromocriptine. *Ann Intern Med* 1984;100:78–91.
22. Johnston DG, Hall K, Kendall-Taylor P, Patrick D, Watson M, Cook DB. Effect of dopamine agonist withdrawal after long-term therapy in prolactinomas. Studies with high-definition computerised tomography. *Lancet* 1984;2:187–192.
23. van 't Verlaat JW, Croughs RJ. Withdrawal of bromocriptine after long-term therapy for macroprolactinomas; effect on plasma prolactin and tumour size [see comments]. *Clin Endocrinol (Oxf)* 1991;34:175–178.
24. Wang C, Lam KS, Ma JT, Chan T, Liu MY, Yeung RT. Long-term treatment of hyperprolactinaemia with bromocriptine: effect of drug withdrawal. *Clin Endocrinol (Oxf)* 1987;27:363–371.
25. Liuzzi A, Dallabonzana D, Oppizzi G, Verde GG, Cozzi R, Chiodini P, Luccarelli G. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985;313:656–659.