

## CLINICAL VIGNETTE

# Case of a Medically Refractory Prolactinoma

Jennifer Han, MD, Sheila Ahmadi, MD, Leili Mirsadraei, MD, William Yong, MD

### Case Report

A 17-year-old female initially presented with a 2-year history of amenorrhea and galactorrhea. Work-up for secondary amenorrhea revealed an elevated prolactin (PRL) level of 22pmol/l (normal <1pmol/l). Magnetic resonance imaging (MRI) demonstrated a “prominent” pituitary and she was initiated on bromocriptine, which she was unable to tolerate due to nausea. She switched to cabergoline, which was initiated at a weekly dose of 0.25mg and titrated to a weekly dose of 1.5mg. Subsequent MRI 6 months later showed an increase in the pituitary mass to 14mm with mild compression of the optic chiasm. PRL never normalized on medical therapy and ranged from 7.7-23pmol/l. She sought evaluation at our institution for persistent amenorrhea despite a 2-year course of medical therapy.

Cabergoline was increased to a weekly dose of 2.5mg. A MRI at our institution confirmed the 10mm pituitary macroadenoma (Figure 1). PRL remained elevated around 8.5pmol/l despite compliance to cabergoline and increases to a weekly dose of 6mg. Despite stepwise increases, PRL remained persistently elevated above 8.5pmol/l and amenorrhea persisted.

She was evaluated by neurosurgery for the medically refractory prolactinoma and underwent a transnasal endoscopic resection given ongoing amenorrhea. Pathology demonstrated positive, often juxtacellular, staining for PRL. Ki-67 nuclear labeling was estimated at 5-7% focally and there was increased P53 staining (Figure 2). The findings were of an atypical sparsely granulated lactotroph adenoma. Her postoperative course was complicated by transient diabetes insipidus. The patient had resumption of menses 8 weeks postoperatively with normalization of prolactin levels.

### Diagnosis

Medically refractory prolactinoma.

### Clinical evidence and unusual features:

Prolactinomas represent 40% of pituitary adenomas and are the second most common etiology for hyperprolactinemia after medications<sup>1-5</sup>. These tumors can be characterized into micro- (<10mm) or macro-prolactinomas (>10mm) and diagnosis is confirmed by gadolinium-enhanced MRI which has higher sensitivity and superior definition compared to computed tomography<sup>6</sup>. Prevalence of prolactinomas is estimated at 100 per million adults and they occur most commonly in women of reproductive age although the incidence in both genders is equal after the age of 50<sup>2, 3, 5, 7</sup>. Endocrinological consequences of hyperprolactinemia include infertility and hypogonadism<sup>1, 3</sup>. Clinically, patients with prolactinomas describe symptoms of galactorrhea, amenorrhea, impotence, change in libido, and neurologic symptoms of headaches, visual impairment or visual field deficits if tumors are large<sup>3-5</sup>. Indications for treatment include sexual dysfunction, and the presence of macroadenomas or increasing microadenomas. Asymptomatic patients with hyperprolactinemia or stable microadenomas may be monitored closely without medical or surgical intervention<sup>5</sup>. Treatment of prolactinomas includes normalization of PRL levels, control of tumor size, and ultimately the improvement of infertility, sexual dysfunction, and prevention of osteoporosis<sup>2, 3</sup>.

Dopamine agonists are the mainstay in treatment for prolactinomas<sup>3, 5</sup>. They interact with the dopamine receptor 2 (DRD2) to inhibit hormone secretion, down-regulate PRL synthesis, and decrease cell proliferation<sup>[3, 8]</sup>. Of the two available agents, cabergoline remains the preferred agent secondary to the longer half-life of the drug of 65h resulting in less frequent medication dosing with improved compliance, minimal adverse effects, and higher affinity for D2 dopamine-binding sites when compared to bromocriptine<sup>1, 5, 9</sup>. However, if pregnancy is desired, bromocriptine is favored due to documented safety and is continued until pregnancy is confirmed<sup>6</sup>.

Conventional doses of bromocriptine range from 2-15mg/day with most patients requiring less than

7.5mg/day but doses as high as 20-30mg/day have been described in cases of treatment resistance<sup>3, 6</sup>. Therapy with cabergoline is initiated at 0.25-0.5mg once or twice weekly with increases in dose on a monthly basis until hyperprolactinemia resolves<sup>3, 5, 7</sup>. Conventional cabergoline doses are 0.25-4mg weekly although 80-90% patients promptly respond to dopamine agonist therapy at low doses of <1.5mg/week<sup>6, 10</sup>. A retrospective study of 122 pts treated with cabergoline for at least one year showed normalization of PRL in 94% of patients with the majority treated with a dose of <1.5mg/ week<sup>11</sup>. Furthermore, utilizing a dose >3.5mg/week showed no improved outcomes<sup>11</sup>.

Adverse effects of dopamine agonists include orthostatic hypotension, gastrointestinal manifestations of nausea and vomiting, and neurological signs of headache and dizziness, although these side effects are less with cabergoline therapy<sup>3, 5, 12</sup>. Valvular dysfunction with treatment of Parkinson's disease with cabergoline has been reported, although treatment for Parkinson's require high doses of cabergoline of approximately 3mg/day<sup>11</sup>. There have been no major side effects, including clinically significant cardiac valvular disease, described in long-term therapy in the usual doses needed for the treatment of hyperprolactinemia. However, occasionally patients may require higher doses of cabergoline and a maximum of 12mg weekly has been described<sup>11, 13</sup>. Current recommendations are to use the lowest effective dose as cumulative doses may also increase the risk of valvular pathology<sup>3, 13</sup>.

10% of prolactinomas are resistant to treatment with dopamine agonist therapy<sup>4, 8, 10, 14</sup>. The definition of resistance treatment is two-part and includes an inability to normalize PRL and to reduce tumor size by at least 50%<sup>15</sup>. Risk factors for resistance are macroadenomas with cavernous sinus invasion and male gender<sup>4, 16</sup>. Other considerations in cases of medical resistance include noncompliance with medications, administration of exogenous estrogen, which may increase resistance in lactotrophs, or the possibility of malignant transformation of prolactinoma into a carcinoma<sup>17</sup>.

Mechanisms for resistance may be linked to the loss or decreased expression of the DRD2 or post-receptor intracellular transduction mechanisms<sup>1, 8, 10</sup>. Fusco et al., in a series of 10 macroprolactinomas, demonstrated the exhibited quantitative mean of DRD2 mRNA levels in dopamine resistant tumors were lower than dopamine sensitive tumors<sup>8</sup>. Moreover, a reduction in DRD2 receptors may

explain the partial resistance of some prolactinomas to dopamine agonists<sup>8</sup>. Histologically, these dopamine agonist resistant tumors are noted to exhibit increased angiogenesis, cellular atypia, increased proliferation, and increased invasiveness<sup>4</sup>. Furthermore, resistance to cabergoline can also be associated with polymorphisms of the DRD2 gene such as the DRD2 Ncol-T+ alleles, which may lead to downstream reduction or dysfunction of the DRD2 messenger RNA or protein<sup>18</sup>.

Treatment approaches for medically resistant prolactinomas include switching to another dopamine agonist or raising the dose of the drug in an incremental fashion if continued response to the drug is observed<sup>11</sup>. In 5% of resistant patients, a progressive increase of dopamine agonist dosing leads to a normalization of PRL levels which suggests a partial resistance to therapy<sup>10</sup>. In cases of drug resistance, medication intolerance, or partial response, transphenoidal surgery or radiation therapy may be a more appropriate option. As there have been no clear advantages of increasing cabergoline to a dose >3.5mg/week, neurosurgical options may also be considered at with dosages exceeding 3.5mg/week<sup>11</sup>.

Transphenoidal surgery is the most common surgical approach in pituitary adenomas with remission rates of 73-90% and recurrence rates of 9-39%, comparable to dopamine agonist therapy<sup>4, 14</sup>. Absolute indications for surgery includes increasing tumor size despite medical treatment, pituitary infarction or hemorrhage, loss of consciousness, worsening vision, cystic prolactinoma, or CSF leak on dopamine agonist<sup>5</sup>. Patients with elevated preoperative PRL levels >21.7pmol/l or macroadenomas have a worse prognosis in terms of remission of disease<sup>14</sup>. For invasive or incompletely resectable tumors, one may need to continue medical therapy after transphenoidal surgery<sup>1</sup>. Complications of pituitary surgery include transient diabetes insipidus, cerebrospinal fluid leak, oculomotor palsy, visual deficit, cerebrovascular accident, and infection such as meningitis<sup>4, 12</sup>.

Gamma knife radiosurgery has also been used in cases of medically and surgically refractory prolactinomas and has achieved normal PRL levels in approximately a third of patients<sup>14</sup>. Adverse effects include cranial nerve palsies and other pituitary deficiencies<sup>14</sup>. Remission rates are lower in patients on concurrent dopamine agonist therapy due to decreased cell cycling and decreased sensitivity to radiation therapy<sup>18</sup>.

Finally, there are other medications for the treatment of medically refractory prolactinomas such as temozolomide, an alkylating chemotherapeutic drug that has been effective in aggressive or metastatic pituitary tumors<sup>3</sup>. Temozolomide has been used in select cases of resistant prolactinomas with decrease in tumor size by at least 50% and normalization of PRL<sup>4</sup>.

In summary, this case illustrates a medically refractory prolactinoma that presented with amenorrhea and galactorrhea. Conventional first-line dopamine agonist therapy did not offer satisfactory control of hyperprolactinemia despite dosage increases. Ultimately, resection of the tumor normalized PRL levels with resumption of menses. Due to elevated ki-67 markers, she is to undergo frequent serial pituitary imaging to assess for recurrence.

### Teaching point

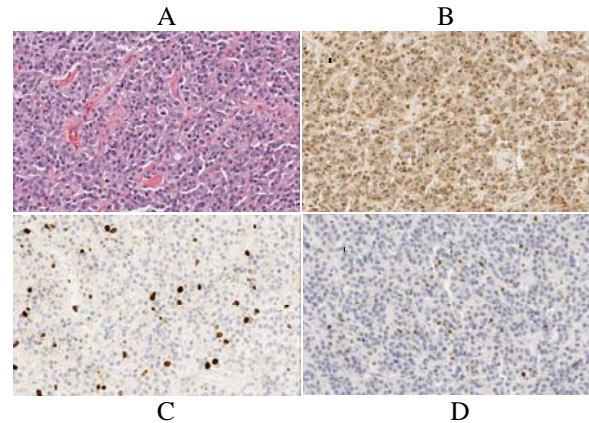
Prolactinomas are a common cause of hyperprolactinemia and can present with mass symptoms and sexual dysfunction. Dopamine agonists are the mainstay of treatment with cabergoline being more effective than bromocriptine. 10% of patients with prolactinomas are resistant dopamine agonist therapy. The definition of resistance is two-part: an inability to normalize PRL and to reduce tumor size by at least 50%. When treating a resistant prolactinoma, one can switch to cabergoline and titrate on a weekly basis until hyperprolactinemia resolves. If weekly dose is >1.5mg and still with evidence of resistance, one can consider surgical therapy. In the cases of medically and surgically resistant prolactinomas, one can consider radiotherapy and/or temozolomide.

### REFERENCES

1. **Hamilton DK, Vance ML, Boulos PT, Laws ER.** Surgical outcomes in hyporesponsive prolactinomas: analysis of patients with resistance or intolerance to dopamine Agonists. *Pituitary*. 2005;8(1):53-60. PubMed PMID: 16411069.
2. **Gillam MP, Molitch ME, Lombardi G, Colao A.** Advances in the treatment of prolactinomas. *Endocr Rev*. 2006 Aug;27(5):485-534. Epub 2006 May 26. Review. PubMed PMID: 16705142.
3. **Colao A, Savastano S.** Medical treatment of prolactinomas. *Nat Rev Endocrinol*. 2011 May;7(5):267-78. doi: 10.1038/nrendo.2011.37. Epub 2011 Mar 22. Review. PubMed PMID: 21423245.
4. **Oh MC, Aghi MK.** Dopamine agonist-resistant prolactinomas. *J Neurosurg*. 2011 May;114(5):1369-79. doi: 10.3171/2010.11.JNS101369. Epub 2011 Jan 7. Review. PubMed PMID: 21214334.
5. **Mann WA.** Treatment for prolactinomas and hyperprolactinaemia: a lifetime approach. *Eur J Clin Invest*. 2011 Mar;41(3):334-42. doi: 10.1111/j.1365-2362.2010.02399.x. Epub 2010 Oct 18. Review. PubMed PMID:20955213.
6. **Ogilvie CM, Milsom SR.** Dopamine agonists in the treatment of prolactinoma: are they still first choice? *Intern Med J*. 2011 Feb;41(2):156-61. doi: 10.1111/j.1445-5994.2010.02410.x. Review. PubMed PMID: 21138511.
7. **Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A.** Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)*. 2006 Aug;65(2):265-73. PubMed PMID: 16886971.
8. **Fusco A, Gunz G, Jaquet P, Dufour H, Germanetti AL, Culler MD, Barlier A, Saveanu A.** Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas. *Eur J Endocrinol*. 2008 May;158(5):595-603. doi: 10.1530/EJE-07-0806. PubMed PMID: 18426817.
9. **Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G.** Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrinol Metab*. 2000 Jun;85(6):2247-52. PubMed PMID: 10852458.
10. **Molitch ME.** Pharmacologic resistance in prolactinoma patients. *Pituitary*. 2005;8(1):43-52. Review. PubMed PMID: 16411068.
11. **Delgrange E, Daems T, Verhelst J, Abs R, Maiter D.** Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. *Eur J Endocrinol*. 2009 May;160(5):747-52. doi: 10.1530/EJE-09-0012. Epub 2009 Feb 17. PubMed PMID:19223454.
12. **Babey M, Sahli R, Vajtai I, Andres RH, Seiler RW.** Pituitary surgery for small prolactinomas as an alternative to treatment with dopamine agonists. *Pituitary*. 2011 Sep;14(3):222-30. doi: 10.1007/s11102-010-0283-y. PubMed PMID: 21170594; PubMed Central PMCID: PMC3146980.
13. **Halperin I, Aller J, Varela C, Mora M, Abad A, Doltra A, Santos AE, Batista E, Garcia-Pavia P, Sitges M, Mirelis JG, Lucas T, Puig-Domingo M.** No clinically significant valvular regurgitation in long-term cabergoline treatment for prolactinoma. *Clin Endocrinol (Oxf)*. 2012 Aug;77(2):275-80. doi: 10.1111/j.1365-2265.2012.04349.x. PubMed PMID: 22288503.
14. **Pouratian N, Sheehan J, Jagannathan J, Laws ER Jr, Steiner L, Vance ML.** Gamma knife radiosurgery for medically and surgically refractory prolactinomas. *Neurosurgery*. 2006 Aug;59(2):255-66; discussion 255-66. PubMed PMID: 16883166.
15. **Molitch ME.** Dopamine resistance of prolactinomas. *Pituitary*. 2003;6(1):19-27. Review. PubMed PMID: 14674720.
16. **Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J.** Sex-related difference in the growth of

- prolactinomas: a clinical and proliferation marker study. *J Clin Endocrinol Metab.* 1997 Jul;82(7):2102-7. PubMed PMID: 9215279.
17. **Molitch ME.** The cabergoline-resistant prolactinoma patient: new challenges. *J Clin Endocrinol Metab.* 2008 Dec;93(12):4643-5. doi: 10.1210/jc.2008-2244. PubMed PMID: 19056842.
18. **Filopanti M, Barbieri AM, Angioni AR, Colao A, Gasco V, Grottoli S, Peri A, Baglioni S, Fustini MF, Pigliaru F, Monte PD, Borretta G, Ambrosi B, Jaffrain-Rea ML, Gasperi M, Brogioni S, Cannavò S, Mantovani G, Beck-Peccoz P, Lania A, Spada A.** Dopamine D2 receptor gene polymorphisms and response to cabergoline therapy in patients with prolactin-secreting pituitary adenomas. *Pharmacogenomics J.* 2008 Oct;8(5):357-63. doi: 10.1038/tpj.2008.1. Epub 2008 Mar 11. PubMed PMID: 18332900.

Submitted on April 26, 2013



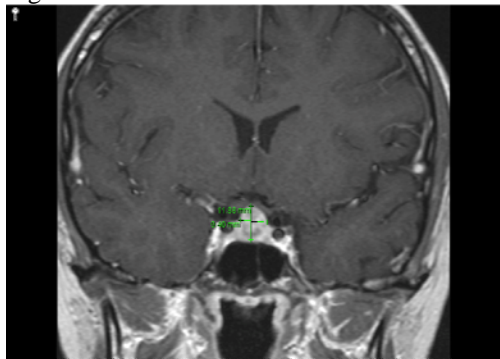
#### Imaging:

- 1) MRI pituitary
- 2) PRL and cabergoline dose

Histopathologic evaluation of the prolactinoma with (a) H&E staining of the tumor shows sheets of chromophobic to lightly acidophilic neuroendocrine cells (b) Immunohistochemistry shows positivity of the tumor for prolactin often as juxtannuclear globules. (c) Ki-67 labeling index is estimated at 5-7% in areas. (d) Nuclear p53 immunostaining is increased. Digital image magnification equivalent: 200x.

#### Figure Legends:

Figure 1.



#### Radiographic imaging of the prolactinoma

(a) Contrast-enhanced brain Computed Tomography (coronal view) a prolactinoma measuring 11.88 X 9.4 mm in size

Figure 2.