

# Ectopic Prolactin Secretion From a Uterine Leiomyoma

Saachi Sachdev,<sup>1</sup> Maria Carolina Reyes,<sup>2</sup> and Peter J Snyder<sup>1</sup>

<sup>1</sup>*Division of Endocrinology, Diabetes and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; and* <sup>2</sup>*Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104*

ORCID numbers: 0000-0002-8247-3287 (S. Sachdev); 0000-0002-9838-3139 (P. J. Snyder).

Ectopic hormone production is well recognized, but ectopic production of prolactin has been reported infrequently. We report here the case of a 47-year-old woman who had hyperprolactinemia (213-224 ng/mL) causing galactorrhea and hypogonadism. Cabergoline treatment, 1.0 mg twice a week, did not lower the prolactin level at all, but excision of a large uterine leiomyoma corrected the hyperprolactinemia and the hypogonadism. The excised leiomyoma tissue exhibited immunostaining for prolactin, confirming by this method for the first time that a uterine leiomyoma was the cause of hyperprolactinemia. This case illustrates the need to consider an ectopic source of prolactin in a patient who has hyperprolactinemia that is not associated with a large sellar mass and is completely resistant to cabergoline.

© Endocrine Society 2020.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

**Key Words:** ectopic prolactin, leiomyoma, dopamine agonist resistant

Ectopic production of hormones is well recognized, but clinically significant hyperprolactinemia due to ectopic production of prolactin is not common. Only a few reports describe hyperprolactinemia associated with uterine leiomyomas [1-4]. We report here a patient who had clinically significant hyperprolactinemia that was corrected by excision of a large uterine leiomyoma. This is the first case in which positive immunostaining for prolactin confirmed that the leiomyoma was the source of the prolactin.

## 1. Case Report

### A. Clinical History

A 47-year old woman presented in June 2018 because of amenorrhea for one year and galactorrhea for one month. She also reported hot flashes and decreased libido. She was not taking prescription medications or dietary supplements. On examination, she had expressible galactorrhea bilaterally. Her serum prolactin concentration was 213 ng/mL (Table 1). Free prolactin was 97.2% of the total. The estradiol was 19 pg/mL, follicle-stimulating hormone (FSH) 5.4 mIU/mL, luteinizing hormone (LH) 1.1 mIU/mL, free thyroxine 1.1 ng/dL, cortisol 11.3 µg/dL, and insulin-like growth factor-1 177 ng/mL (Z score, 0.5). (All laboratory tests were performed at Quest Diagnostics, Horsham, PA.) Magnetic resonance imaging

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging.

Received 2 February 2020

Accepted 11 March 2020

First Published Online 16 March 2020

Corrected and Typeset 9 April 2020.

April 2020 | Vol. 4, Iss. 4

doi: 10.1210/edso/bvaa035 | Journal of the Endocrine Society | 1-4

**Table 1. Prolactin and Estradiol Responses to Cabergoline and Hysterectomy in a Woman Whose Uterine Leiomyoma Caused Hyperprolactinemia**

| Date     | Prolactin<br>(ng/mL) | Estradiol<br>(pg/mL) | Cabergoline Dose<br>(mg/week) |
|----------|----------------------|----------------------|-------------------------------|
| 6/22/18  | 213                  | 20                   | -                             |
| 8/3/18   | 203                  | -                    | 1.0                           |
| 10/12/18 | 213                  | 16                   | 2.0                           |
| 6/24/19  | 224                  | 18                   | -                             |
| 8/14/19  |                      | Hysterectomy         |                               |
| 9/20/19  | 2.5                  | -                    | -                             |
| 11/5/19  | 8.9                  | 114                  | -                             |

(MRI) revealed a sella turcica that was slightly large but a pituitary gland that was small and flattened against the sellar floor.

She was treated with cabergoline, 0.5 mg twice a week, and 6 weeks later, the prolactin level remained elevated, 203 ng/mL (Table 1), so the dose was increased to 1.0 mg twice a week. Ten weeks later, the prolactin level remained elevated, 213 ng/mL, so cabergoline was discontinued. Seven months later, the prolactin level was 224 ng/mL.

During the time that the hyperprolactinemia was being evaluated, her gynecologist was monitoring her for a uterine leiomyoma. When ultrasonography showed that the leiomyoma had increased from  $8.3 \times 8.6 \times 9.8$  cm in June 2018 to  $13.9 \times 10.4 \times 11.8$  cm in June 2019, the gynecologist performed a total abdominal hysterectomy and salpingectomy but not ovariectomy. One month after surgery, the galactorrhea and hot flashes had resolved, and the prolactin level was normal, 2.5 ng/mL (Table 1). Six weeks later, the prolactin level remained normal, 8.7 ng/mL, and the estradiol level had increased to normal, 114 pg/mL, accounting for resolution of her hot flashes. The FSH was 3.7 mIU/mL, and LH was 4.9 mIU/mL.

### B. Pathological Examination and Immunohistochemical Staining (Fig. 1)

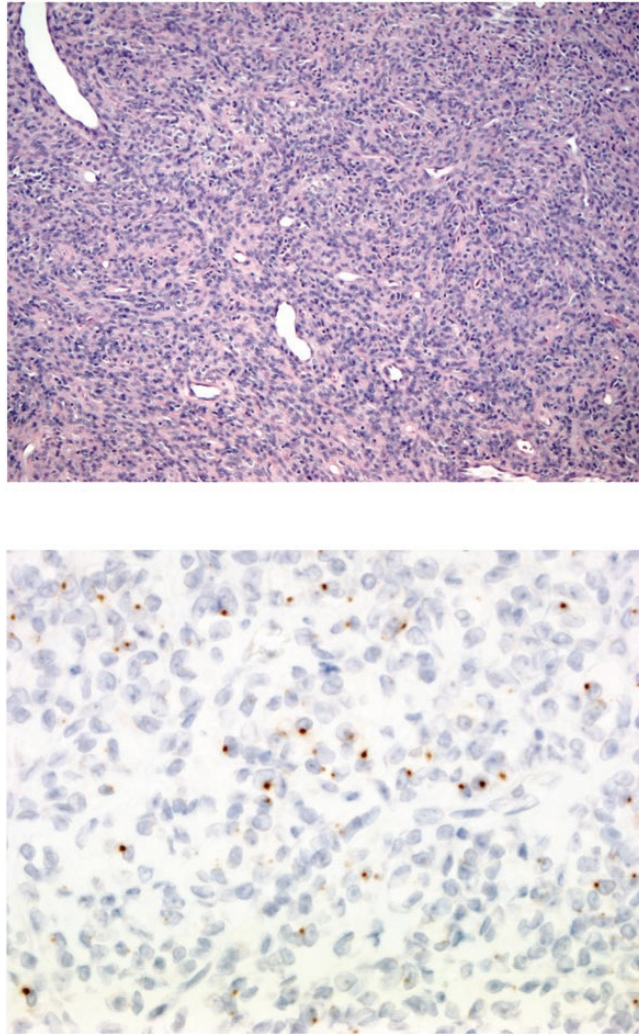
Pathological examination showed that the excised uterus contained a  $12 \times 10 \times 6$  cm mass. Hematoxylin and eosin staining of sections of the mass showed a neoplasm composed of a dense proliferation of spindle cells growing in a fascicular pattern admixed with thick-walled vessels, consistent with smooth muscle. Cell nuclei were elongated and ovoid. There was no evidence of increased mitotic activity or tumor cell necrosis. Immunohistochemical staining for prolactin showed focal but intense, positive punctuate staining.

## 2. Discussion

A 47-year-old woman had persistent clinically significant hyperprolactinemia that was resistant to cabergoline but that resolved completely after excision of a large uterine leiomyoma. Immunocytochemical staining confirmed that the leiomyoma was the source of the excessive production of prolactin.

Hormone secretion from an ectopic site is well recognized and is usually of single chain peptide hormones. Clinically significant ectopic hormone production by a uterine leiomyoma is uncommon, but secretion of parathyroid hormone-related peptide [5] and erythropoietin [6], as well as prolactin [1-4], have been reported. Ectopic prolactin production has also been reported from other tumors, including gonadoblastoma [7], ovarian teratoma [8], perivascular epithelioid cell tumor [9], uterine cervical carcinoma [10], and colorectal adenocarcinoma [11].

Although uterine leiomyomas have rarely been reported to cause hyperprolactinemia, cultured leiomyoma cells [12, 13], cell lines derived from leiomyoma muscle cells [14], and even normal myometrial cells in culture [15, 16] have been shown to produce prolactin



**Figure 1.** Pathologic examination of a large leiomyoma excised from a 47-year-old woman who had hyperprolactinemia. The upper panel shows hematoxylin and eosin staining, demonstrating dense proliferation of spindled cells growing in a fascicular pattern. The lower panel shows immunostaining for prolactin, demonstrating focal but intense positive cytoplasmic staining.

messenger ribonucleic acid and to secrete immunoreactive prolactin into culture medium. The secreted prolactin is similar to that secreted by the pituitary gland immunologically, as shown by parallel dilution curves, and by size, as shown by gel filtration chromatography [12, 13]. Synthetic thyrotropin-releasing factor (TRH), however, did not stimulate prolactin secretion [14].

The patient presented here is similar in many ways to the few cases previously reported of patients who had hyperprolactinemia associated with a uterine leiomyoma: hyperprolactinemia of a modest degree (<250 ng/mL), but persistent and causing hypogonadism; resistance to dopamine agonist treatment; and cure of hyperprolactinemia by surgical excision of the leiomyoma [1-4]. Also similar to previously reported cases, this patient's leiomyoma was very large, >8 cm in diameter, suggesting that these tumors produce and secrete prolactin inefficiently [1-4]. In the patient presented here, for the first time, immunostaining confirmed that the leiomyoma was the source of the prolactin.

The significance of this case is that it illustrates the need to consider ectopic prolactin secretion when hyperprolactinemia occurs in the absence of a pituitary macroadenoma and is completely resistant to dopamine agonist treatment. The vast majority of patients who have

hyperprolactinemia as the result of a lactotroph adenoma experience a reduction in prolactin in response to dopamine agonist treatment. Although a well-documented minority of patients who have lactotroph adenomas exhibit some degree of resistance to dopamine agonist treatment, most lactotroph adenomas that are resistant are >1 cm in diameter and, therefore, recognizable by MRI, and are only relatively resistant in that increasing doses of cabergoline do reduce prolactin levels to some degree [17]. When hyperprolactinemia is the result of most other causes, such as stalk compression, the lactotroph cells are normally responsive to cabergoline.

We conclude that finding hyperprolactinemia that is not associated with a large sellar mass and is completely resistant to cabergoline treatment warrants consideration of an ectopic source of prolactin secretion, such as a uterine leiomyoma.

## Additional Information

**Correspondence:** Peter J. Snyder, Smilow 12-135, 3400 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: [pjs@penncmedicine.upenn.edu](mailto:pjs@penncmedicine.upenn.edu).

**Disclosure Summary:** The authors have nothing to disclose.

**Data Availability:** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

---

## References

1. Cordiano V. Complete remission of hyperprolactinemia and erythrocytosis after hysterectomy for a uterine fibroid in a woman with a previous diagnosis of prolactin-secreting pituitary microadenoma. *Ann Hematol.* 2005;**84**(3):200-202.
2. Herzog AG. Migraine with ectopic hyperprolactinemia from uterine fibroids. *Neurology.* 2000;**55**(1):148-149.
3. Sendur SN, Aktoz F, Usubutun A, Tuncer ZS, Erbas T. Hyperprolactinaemia associated with giant uterine myoma, description of a case and review of literature. *J Obstet Gynaecol.* 2019;**39**(7):1034-1036.
4. Sato H, Asami Y, Shiro R, et al. Resolution of dopamine agonist-resistant hyperprolactinemia by hysterectomy: a case report. *Gynecol Endocrinol.* 2018;**34**(3):199-201.
5. Ravakhah K, Gover A, Mukunda BN. Humoral hypercalcemia associated with a uterine fibroid. *Ann Intern Med.* 1999;**130**(8):702.
6. Yoshida M, Koshiyama M, Fujii H, Konishi M. Erythrocytosis and a fibroid. *Lancet.* 1999;**354**(9174):216.
7. Hoffman WH, Gala RR, Kovacs K, Subramanian MG. Ectopic prolactin secretion from a gonadoblastoma. *Cancer.* 1987;**60**(11):2690-2695.
8. Kallenberg GA, Pesce CM, Norman B, Ratner RE, Silverberg SG. Ectopic hyperprolactinemia resulting from an ovarian teratoma. *JAMA.* 1990;**263**(18):2472-2474.
9. Korytnaya E, Liu J, Camelo-Piragua S, Sullivan S, Auchus RJ, Barkan A. Ectopic prolactin secretion from a perivascular epithelioid cell tumor (PEComa). *J Clin Endocrinol Metab.* 2014;**99**(11):3960-3964.
10. Hsu CT, Yu MH, Lee CY, Jong HL, Yeh MY. Ectopic production of prolactin in uterine cervical carcinoma. *Gynecol Oncol.* 1992;**44**(2):166-171.
11. Bhatavdekar JM, Patel DD, Chikhlikar PR, et al. Ectopic production of prolactin by colorectal adenocarcinoma. *Dis Colon Rectum.* 2001;**44**(1):119-127.
12. Daly DC, Walters CA, Prior JC, et al. Prolactin production from proliferative phase leiomyoma. *Am J Obstet Gynecol.* 1984;**148**(8):1059-1063.
13. Chapitis J, Riddick DH, Betz LM, et al. Physicochemical characterization and functional activity of fibroid prolactin produced in cell culture. *Am J Obstet Gynecol.* 1988;**158**(4):846-853.
14. Nowak RA, Rein MS, Heffner LJ, Friedman AJ, Tashjian AH Jr. Production of prolactin by smooth muscle cells cultured from human uterine fibroid tumors. *J Clin Endocrinol Metab.* 1993;**76**(5):1308-1313.
15. Walters CA, Daly DC, Chapitis J, et al. Human myometrium: a new potential source of prolactin. *Am J Obstet Gynecol.* 1983;**147**(6):639-644.
16. Gellersen B, Bonhoff A, Hunt N, Bohnet HG. Decidual-type prolactin expression by the human myometrium. *Endocrinology.* 1991;**129**(1):158-168.
17. Melmed S, Casanueva FF, Hoffman AR, et al.; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;**96**(2):273-288.