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Case Report

Prolactinoma and Adenomyosis – More than Meets the Eye: A Case Report

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ABSTRACT

Background/Objective: To report a case of adenomyosis in a woman with hyperprolactinemia which resolved after initiation of dopamine agonist therapy.
Case Report: A 35-year-old woman with a history of Graves' disease was referred for evaluation of hyperthyroidism in March 2020. She was started on methimazole and thyroid function normalized. The patient also had a history of a pituitary microadenoma and was previously treated with cabergoline which was stopped after 12 months as she became pregnant.
In July 2020, the patient began to have polymenorrhea. Hyperprolactinemia was thought to be an unlikely cause as it most often causes hypogonadotropic hypogonadism with amenorrhea. A pelvic ultrasound demonstrated a bulky uterus with adenomyosis. Gynecology recommended treating adenomyosis by lowering her prolactin levels. She was started on cabergoline 0.25 mg weekly in October 2021. Within 2 months of initiation of cabergoline, she had resolution of symptoms and radiological resolution of adenomyosis.
Discussion: Prolactin has been implicated in the pathogenesis of adenomyosis, endometriosis and leiomyomas suggesting that a decrease in prolactin levels may suppress these lesions. The pathogenesis of adenomyosis has been related to direct prolactin effects in the promotion of gland/cell proliferation and function.
Conclusion: We conclude that prolonged elevation in prolactin may result in the development of adenomyosis and subsequent prolonged abnormal uterine bleeding. Dopamine agonists, like cabergoline, inhibit the synthesis and secretion of prolactin from the pituitary gland and may have a role in the management of adenomyosis in patients with hyperprolactinemia.

Introduction

Hyperprolactinemia is a common diagnosis especially in premenopausal women, most commonly due to pituitary macroprolactinoma. It often presents with galactorrhea, and secondary amenorrhea due to altered gonadotropin-releasing hormone (secretion secondary to increased prolactin). Adenomyosis is not an expected finding in patients with hyperprolactinemia. In this paper, we report a case of adenomyosis in a woman with hyperprolactinemia which resolved after initiation of dopamine agonist therapy.

Case Report

This case report details an uncommon presentation of hyperprolactinemia and an unexpected effect of dopamine agonist therapy (Table). Informed consent was obtained from the patient. A 35-year-old woman with a history of Graves' disease was referred to an endocrinology clinic for evaluation of hyperthyroidism in March 2020 (she was not pregnant, postpartum or

Abbreviations: VEGF, vascular endothelial growth factor.

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lactating during this time). She was diagnosed with Graves' disease at age 29 (in 2014) during pregnancy and was treated with antithyroidal agents for approximately 24 months.

She had been experiencing fatigue, headaches and oligomenorrhea for several months. Given her history of Graves' disease and biochemical evidence of recurrent hyperthyroidism (Table 1), she was started on methimazole 2.5 mg daily. Her symptoms were attributed to hyperthyroidism.

Four months later (July 2020), the patient had improvement in fatigue and headaches, however, she described having polymenorrhea with menstrual bleeding every 2 weeks, lasting a week each time. She was prescribed 10-day course of progesterone in an attempt to induce a withdrawal bleed and to help regulate her cycles. The patient reported regular menses (every 5 weeks) after she took progesterone.

The patient also had a history of pituitary microadenoma. She had presented at age 25 with a 1-year history of oligomenorrhea and was found to have an elevated prolactin level (100 ug/L). Magnetic resonance imaging demonstrated a 4 mm pituitary microadenoma. She was started on cabergoline 0.5 mg weekly which was stopped after 12 months as she became pregnant.

Her prolactin level in July 2020 was mildly elevated at 32.5 ug/L. The patient was on no other medications that could affect prolactin levels. An magnetic resonance imaging sella was completed in November 2020 to assess for changes in the size of the microprolactinoma which was reported as "no larger than 5 mm"(Fig. 1).

In April 2021, the patient began to have polymenorrhea once again. Hyperprolactinemia was thought to be an unlikely culprit as it most often causes hypogonadotropic hypogonadism with amenorrhea. She had been euthyroid for several months therefore hyperthyroidism was not thought to be contributing. Hyperandrogenism was ruled out as a possible cause of irregular menses. Therefore, she was referred to gynecology for further evaluation of abnormal uterine bleeding.

Due to the COVID-19 pandemic, gynecological evaluation was delayed. A pelvic ultrasound in October 2021 demonstrated a bulky uterus with adenomyosis (Fig. 2). Accordingly, the recommendation was made to treat adenomyosis by lowering her prolactin levels. She was started on cabergoline 0.25 mg weekly in October 2021, 15 months following the onset of polymenorrhea. Cabergoline was chosen as treatment due to its greater tolerability, once weekly administration and recommendation by the patient's obstetrician based on their prior experience and animal data. Within 2 months of initiation of cabergoline, she had resolution of symptoms and radiological resolution of adenomyosis. We plan on continuing cabergoline until there is radiologic resolution of microprolactinoma.

Highlights

- Prolactin elevation may result in the development of adenomyosis.
- Adenomyosis may cause abnormal bleeding in patients with hyperprolactinemia.
- Dopamine agonists may treat adenomyosis caused by hyperprolactinemia.

Clinical Relevance

We describe that prolonged elevation in prolactin may result in the development of adenomyosis and subsequent prolonged abnormal uterine bleeding. Dopamine agonists, like cabergoline, inhibit the synthesis and secretion of prolactin from the pituitary gland and may have a role in the management of adenomyosis in patients with hyperprolactinemia.

Discussion

The pathogenesis of adenomyosis is unclear to date, however, currently accepted hypotheses include microtrauma of the endometrial-myometrial interface resulting in invasion of the endometrium into the myometrium , induction of adenomyotic lesions by aberrant local steroid and pituitary hormones, and inflammatory molecules.[1]

Prolactin plays an important role within the reproductive system and elevated prolactin levels inhibit gonadotropin-releasing hormone secretion and result in decrease in both luteinizing hormone and follicle stimulating hormone.[2] This leads to hypogonadism in men and women.[2] Prolactin has been implicated in the pathogenesis of adenomyosis, endometriosis and leiomyomas suggesting that a decrease in prolactin levels may suppress these lesions. The pathogenesis of adenomyosis has been related to direct prolactin effects in the promotion of gland/cell proliferation and

Table
Timeline depicting clinical, laboratory and diagnostic imaging findings, and medication

Year	2020		2021				2022
Month	March	July	January	April	September	November	January
Clinical findings							
Menstrual cycle length	5 wk	2 wk then every 5 wk post progesterone		2 wk			4 wk
Laboratory findings							
Prolactin (ng/mL)		32.5	39.1	28.5	39.9	35.3	7.2
TSH (uIU/mL)	<0.01	0.02	1.37	0.71	0.82	1.37	0.8
fT3 (mcg/dL)	6.1	4.2		3.7			4.3
fT4 (mcg/dL)	20	9.5		12			13
LH (IU/L)				13.2			
FSH (IU/L)				7			
Estradiol (pg/mL)				228			
Diagnostic imaging findings							
		MRI sella: micro adenoma <0.5 cm			Transvaginal US: adenomyosis		Sonohysterogram: resolution of adenomyosis
Medication							
	Methimazole 2.5 mg per day					Cabergoline 0.25 mg per week	

Abbreviations: FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid stimulating hormone.

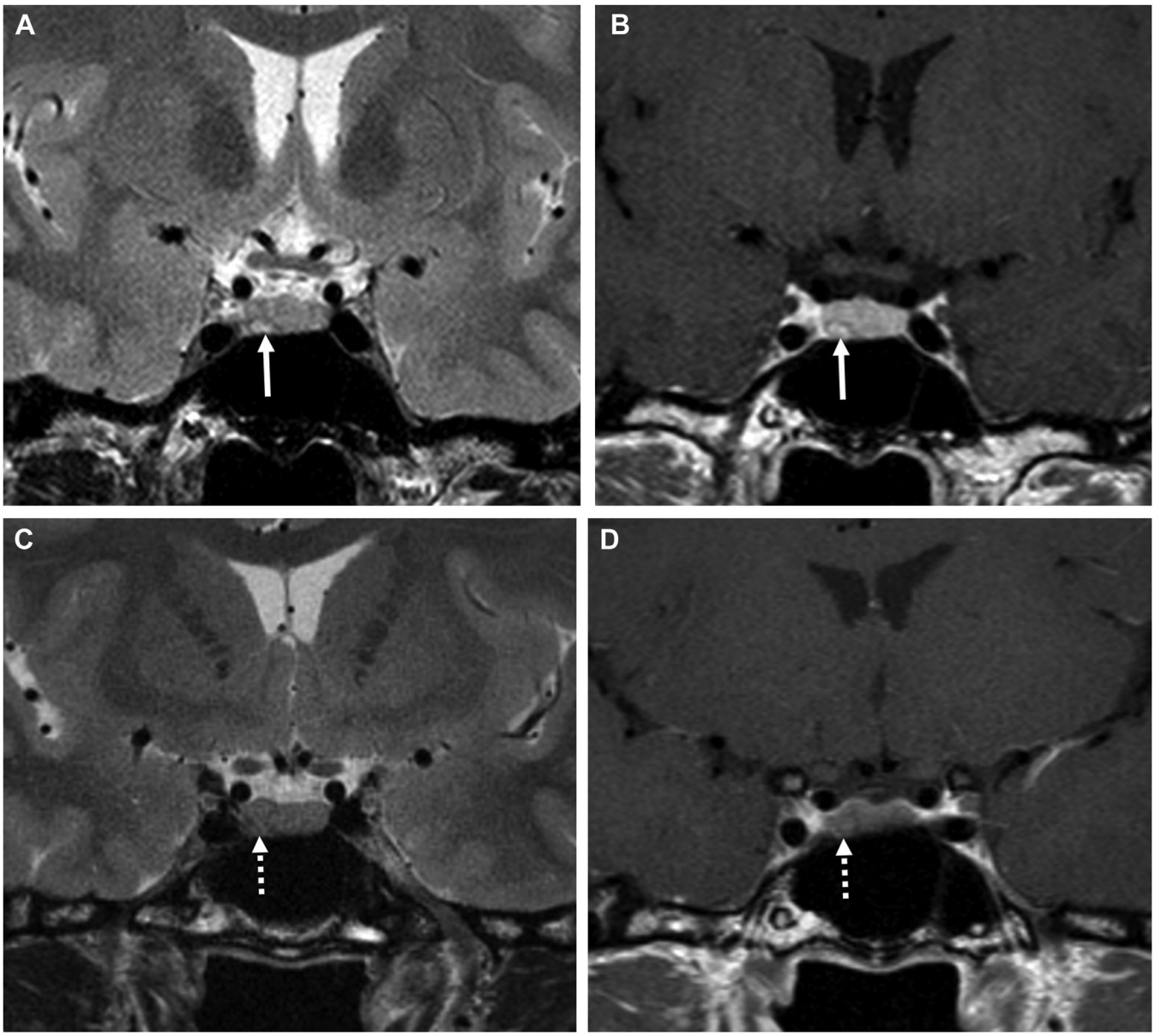

Fig. 1. MRI Sella. *A* and *B*: MRI sella from 2011 showing small lesion in the *Right* inferior aspect of the pituitary gland that is (*A*) hyperintense on T2 weighted image (T2WI) and (*B*) hyperenhancing on post-contrast T1WI. *C* and *D*: MRI sella from 2020 showed evolution in signal within the lesion, now mostly (*C*) isointense compared to the rest of the pituitary gland on T2WI and (*D*) post-contrast T1WI.

function.[2] In mice models, intrauterine pituitary isograft implantation has been observed to induce adenomyosis.[3] Also, a high incidence of adenomyosis has been observed to be associated with elevated circulating prolactin levels.[3] Thus, it is hypothesized that prolactin may be implicated in adenomyosis induction.[3] Furthermore, administration of a dopamine agonist, bromocriptine, to mice models with pituitary isografts resulted in the complete suppression of the induction of uterine adenomyosis.[4]

Another potential reason for the improvement of adenomyosis is the inhibition of angiogenesis. Vascular endothelial growth factor (VEGF) induces angiogenesis of immature blood vessels.[5] Dopamine agonists, such as cabergoline, promote endocytosis of VEGF receptor-2 in endothelial cells and thus prevent VEGF receptor-2 binding and reduce angiogenesis.[5] In 2009, Novella-Maestre and colleagues[5] investigated the anti-angiogenic properties of cabergoline on the growth of established endometriosis lesions in animal models. Following treatment, a significant decrease in the percentage of active endometriotic lesions and cellular proliferation index was observed. In another study conducted in 2011, patients with endometriosis and hyperprolactinemia were treated with quinagolide, a dopamine agonist, which resulted in a decrease in the size of endometriotic lesion as well as the production of VEGF and the density of the VEGF receptor-2.[6] Although endometriosis and adenomyosis are clinically different diseases, they share some disease characteristics and treatment methods. For example, both of these diseases present with severe pelvic pain, and originate from ectopic endometrial tissue. Therefore, this patients' adenomyosis may have also been improved by dopamine agonist therapy through the inhibition of angiogenesis.

Conclusion

We report a case of adenomyosis in a patient with a history of Graves' disease and hyperprolactinemia due to a

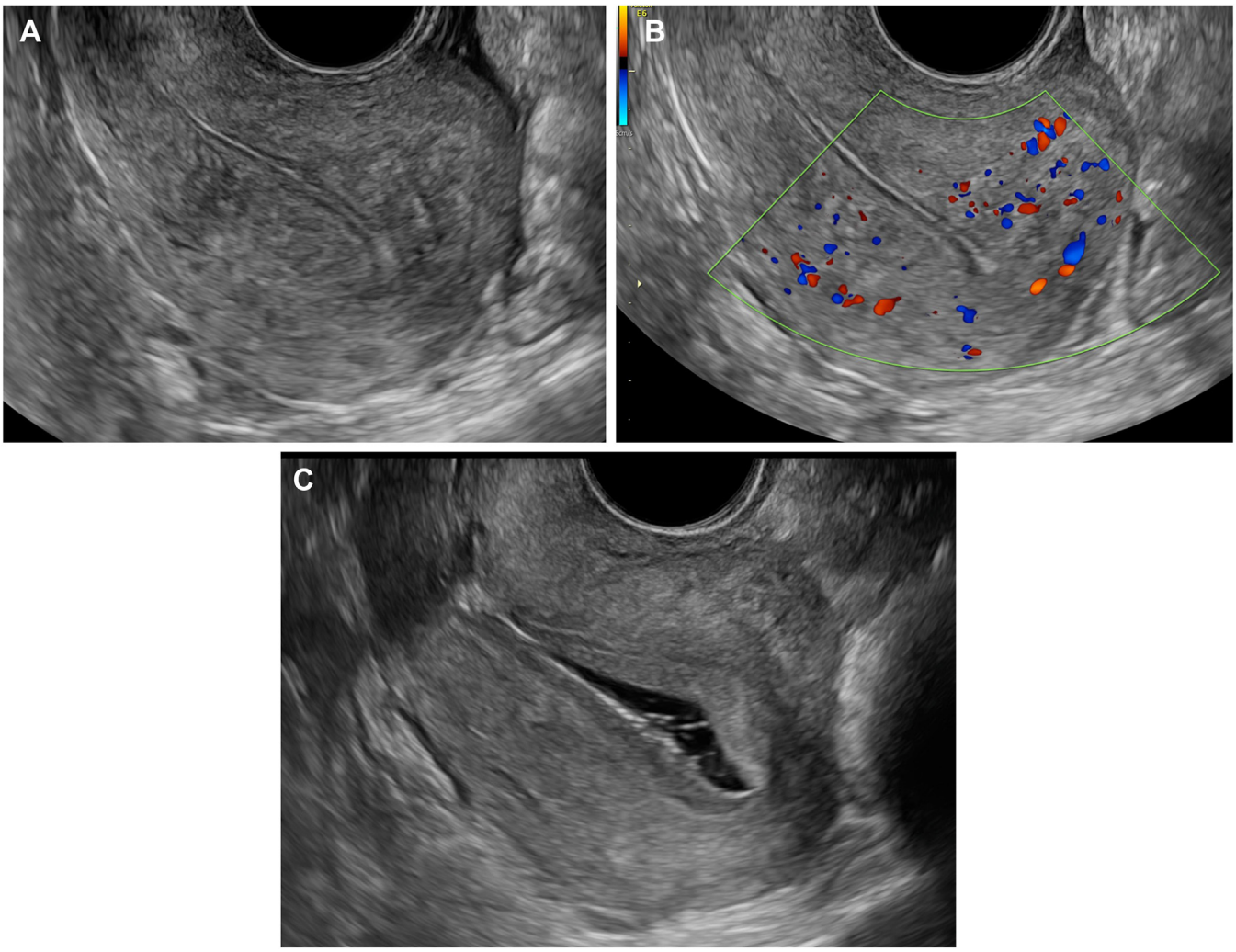

Fig. 2. Pelvic Ultrasound. *A* and *B*: Retroverted uterus with inhomogeneous myometrial echotexture and indistinct endometrial stripe = diffuse adenomyosis. Increased vascularity of myometrium. *C*: Post Rx. Homogeneous myometrial echotexture with smooth endometrial-myometrial interface

microprolactinoma. Her prolonged elevation in prolactin may have resulted in the development of adenomyosis and subsequent prolonged abnormal uterine bleeding. Dopamine agonists, like cabergoline, inhibit the synthesis and secretion of prolactin from the pituitary gland and may have played a role in the resolution of adenomyosis in this patient.

This case highlights the importance of recognizing adenomyosis as a potential cause of abnormal uterine bleeding in patients with hyperprolactinemia. Dopamine agonists have anti-angiogenic and antiprolactin effects and were successful in the treatment of adenomyosis caused by hyperprolactinemia in this case.

To date, there are no international guidelines to follow for surgical or medical treatment of adenomyosis. This is of great importance for future research as the disease requires a lifelong management plan, including bleeding and pain control, preserving fertility, and pregnancy outcomes. Furthermore, as a clear and causative role for prolactin in the pathogenesis of adenomyosis is yet to be determined, further research is needed to elucidate this relationship as well as evaluate the effect of dopamine agonists as a targeted therapy for patients with hyperprolactinemia and adenomyosis.

Conflict of interest

The authors have no multiplicity of interest to disclose.

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