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Case Report

Functional Suppression of a Prolactinoma by a Dopamine-Secreting Paraganglioma

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Abstract

Prolactin-secreting pituitary adenomas are typically treated with dopamine agonists to inhibit prolactin secretion and reduce tumor size. Dopamine-secreting paragangliomas are rare neuroendocrine tumors of sympathetic and parasympathetic paraganglia and often do not provoke symptoms of catecholamine excess. Although overlapping genetic drivers have been described for paragangliomas and pituitary adenomas, biochemical crosstalk between coexisting tumors is underexplored. We describe the case of a 52-year-old male individual who presented with cerebrospinal fluid (CSF) rhinorrhea and was found to have an invasive, 4.2-cm pituitary mass with modestly elevated prolactin (130.9 ng/mL [130.9 µg/L], reference range [RR] 2-18 ng/mL [2-18 µg/L]). Additional imaging discovered a mediastinal mass suspicious for a thoracic paraganglioma. Biochemical screening demonstrated marked elevation of plasma and urinary dopamine. Following paraganglioma resection, dopamine levels normalized, but prolactin rose significantly (877.8 ng/mL [877.8 µg/L]), suggesting an endogenous dopamine agonist–like effect from the paraganglioma to suppress pituitary prolactin hypersecretion. Pituitary pathology was notable for a PIT1 (pituitary transcription factor-1)-lineage pituitary adenoma with absent immunohistochemical staining for prolactin. Genetic testing found a previously unreported germline *SDHC* variant of uncertain significance. In this case, we report a novel biologic signaling mechanism between 2 rare primary endocrine tumors and highlight challenges in their diagnosis and management.

Key Words: prolactinoma, hyperprolactinemia, dopamine, paraganglioma, SDHB, PIT1 pituitary adenoma

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; DOTATATE PET/CT, DOTATATE positron electron tomography/computed tomography; MRI, magnetic resonance imaging; PIT1, pituitary transcription factor-1; PPGL, pheochromocytoma/paraganglioma; RR, reference range; SDH, succinate dehydrogenase; VUS, variant of unknown significance.

Introduction

Prolactinomas are benign pituitary tumors that arise from anterior pituitary lactotroph cells and secrete excess prolactin. The primary complications of prolactinomas relate to their size and the presence of symptoms caused by hyperprolactinemia. Clinical practice guidelines typically recommend dopamine agonist therapy to lower prolactin levels and decrease tumor size in patients with large or symptomatic prolactinomas. Surgery is typically reserved for patients with insufficient biochemical or anatomical response to maximally tolerated dopamine agonist treatment [1].

Pheochromocytomas and paragangliomas (PPGLs) are neuroendocrine tumors that arise from chromaffin cells and develop within the adrenal medulla or sympathetic or parasympathetic paraganglia respectively. PPGLs may be functionally silent or exhibit adrenergic, noradrenergic, dopaminergic, or mixed secretory phenotype [2]. It is critical to diagnose and, when appropriate, resect PPGLs because of the risk of complications associated with catecholamine excess, local mass effects, and malignant potential [3].

While both PPGLs and pituitary adenomas are capable of secreting hormones in excess, the clinical and molecular characterization of these functional tumors in coexistence is scarce. In this report, we present the evaluation and treatment challenges of a patient diagnosed with synchronous dopamine-secreting thoracic paraganglioma and prolactin-secreting pituitary adenoma. We outline genetic and histologic findings and present the clinical and hormonal interplay between these 2 functional tumors, which has not been described in current literature but resonates well within the known hypothalamus-pituitary-prolactin axis physiology and feedback mechanisms.

Case Presentation

A 52-year-old male individual presented with a 6-month history of clear, thin rhinorrhea with positional head changes. He did not have any preceding head trauma and denied headaches or vision changes. Review of systems was positive for low libido and negative for heart palpitations, sweating,

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dizziness, or lightheadedness. Hypertension was diagnosed many years earlier, but he only took antihypertensive medication over the past year. His blood pressure was uncontrolled on lisinopril and metoprolol succinate. Other medications included levothyroxine for hypothyroidism. His father and sister both had essential hypertension. The patient had 2 sons; one had mild hypertension, but both were reported to be in good health otherwise. A thorough family history was negative for benign or malignant tumors. The patient had 2 prior uncomplicated and unrelated surgeries.

Diagnostic Assessment

At initial assessment, the patient's blood pressure was elevated to 172/100 mmHg, and heart rate was 88 beats per minute. Physical examination was notable for reproducible rhinorrhea with leaning forward, concerning for cerebrospinal fluid (CSF) leak. Brain imaging demonstrated a highly invasive, $4.2 \times 3.2 \times 3.1$ cm sellar mass with suprasellar extension, superior displacement of the optic chiasm, bilateral sphenoid sinus invasion, and left cavernous sinus invasion with encasement of the left internal carotid artery (Fig. 1A and 1B). Formal visual field testing was normal. Pituitary hormone profiling revealed hyperprolactinemia (prolactin 130.9 ng/mL [130.9 µg/L], reference range [RR]: 2-18 ng/mL [2-18 µg/L], performed with serial dilution to exclude hook effect, Table 1) and hypogonadotropic hypogonadism. Free thyroxine (FT4) on levothyroxine, cortisol, and insulin-like growth factor 1 (IGF-1) levels were normal. As the prolactin level was lower than expected for a prolactinoma of this size, pituitary metastasis from an undiagnosed primary malignancy was considered. Subsequent chest computed tomography (CT) scan revealed a 4.7-cm heterogeneously enhancing left anterior mediastinal mass concerning for a paraganglioma (Fig. 2A). Plasma catecholamine and catecholamine metabolite testing was significant for dopamine elevation to more than 100 times the upper limit of normal (2531 pg/mL [16 522 pmol/L], RR < 36.7 pg/mL [<240 pmol/L]). Plasma metanephrine, normetanephrine, epinephrine, and norepinephrine levels were normal. His 24-hour urine testing also showed the dopamine fraction approximately 3.5 times the upper limit of normal, as well as slightly elevated norepinephrine and normetanephrine fractions (Table 1). Gallium-68 DOTATATE positron electron tomography/CT scan (^{68}Ga-DOTATATE PET/CT) did not demonstrate sites of disease (Fig. 2B-2D) other than the mediastinal and pituitary masses.

Germline sequencing for hereditary PPGL susceptibility genes was negative for *MEN1*, *RET*, *NF1*, *VHL*, *SDHB*, and *SDHD* (among others) mutations but did identify a monoallelic variant of uncertain significance (VUS) in *SDHC* (*SDHC* c.155T>C; [p.Leu52Pro]) that was predicted to be pathogenic based on prediction modeling programs (Invitae, SIFT, PolyPhen-2).

Treatment

Due to persistent hypertension, he was started on alpha blockade with doxazosin 1 mg twice a day and underwent left thoracotomy for paraganglioma resection. Vasopressors were required intraoperatively but were weaned off on emergence from anesthesia. Given the presence of a germline *SDHC* VUS, succinate dehydrogenase (SDH) B (SDHB) immunohistochemistry was performed on the paraganglioma tissue and was normally retained (Fig. 3).

Following paraganglioma resection, plasma and urine dopamine and all other catecholamine and metabolite levels normalized. However, 2 weeks after paraganglioma surgery, his serum prolactin level rose dramatically to 877.8 ng/mL (877.8 µg/L), more than 6-fold presurgery levels. The pituitary mass was now felt to be consistent with a prolactinoma. Due to technical concerns with pituitary surgery, he was cautiously started on cabergoline 0.25 mg twice weekly, which decreased prolactin to mildly elevated range (25.8 ng/mL [25.8 µg/L], RR 2-18 ng/mL [2-18 µg/L]). One month later, the pituitary tumor size was unchanged on magnetic resonance imaging (MRI), but he developed worsening CSF leak symptoms. Cabergoline was discontinued, and he promptly underwent transsphenoidal surgery for CSF leak repair and partial resection of approximately 20% of the pituitary mass. Multiple areas of the tumor were assessed on pathology, which revealed a pituitary transcription factor-1 (PIT1)-positive pituitary adenoma with Ki-67 (MIB-1) proliferation index of <1%, negative staining for steroidogenic factor 1 (SF1), T-box transcription factor (TPIT), prolactin, growth hormone (GH), and thyroid-stimulating hormone (TSH), and normal SDHB staining (Fig. 4). Cabergoline was resumed and uptitrated 2 months following pituitary surgery due to recurrence of mild hyperprolactinemia.

Outcome and Follow-Up

Since his paraganglioma resection, the patient's plasma and 24-hour urine dopamine levels remain normal. Chest imaging shows no recurrence at 1 year following surgery. His blood pressure is better controlled on medication. Rhinorrhea resolved after CSF leak repair, and his prolactin remains in low-normal range on cabergoline 0.5 mg twice weekly. Testosterone replacement therapy was started due to persistent hypogonadism. He continues without headaches, visual field deficits, or neurologic dysfunction. Pituitary MRI done 6 months following pituitary surgery showed decreased tumor bulk but similar extension to and encasement of regional structures (Fig. 1C and 1D). Radiation therapy was discussed with the patient, but as he remains asymptomatic, he elected to continue treatment with cabergoline alone, for the time being, to maintain prolactin suppression and encourage further tumor shrinkage.

Discussion

Prolactin secretion from pituitary lactotrophs is inhibited by dopamine via negative feedback. While structural insult or compression of the pituitary stalk ("stalk effect") from nonfunctional pituitary tumors can cause modest hyperprolactinemia, prolactin concentrations >200 ng/mL [>200 µg/L] are typically associated with prolactinoma only [1]. Giant macroprolactinomas (> 4 cm) are associated with prolactin concentrations greater than 1000 ng/mL [1000 µg/L] [4]. The patient's initial prolactin level (130.9 ng/mL [130.9 µg/L]) prior to paraganglioma resection was much lower than expected for a typical prolactinoma of his size, which raised suspicion for a poorly functional or less well-differentiated prolactinoma or other nonfunctional sellar mass. However, the subsequent 6-fold rise of prolactin 2 weeks following paraganglioma surgery indicated that endogenous dopamine

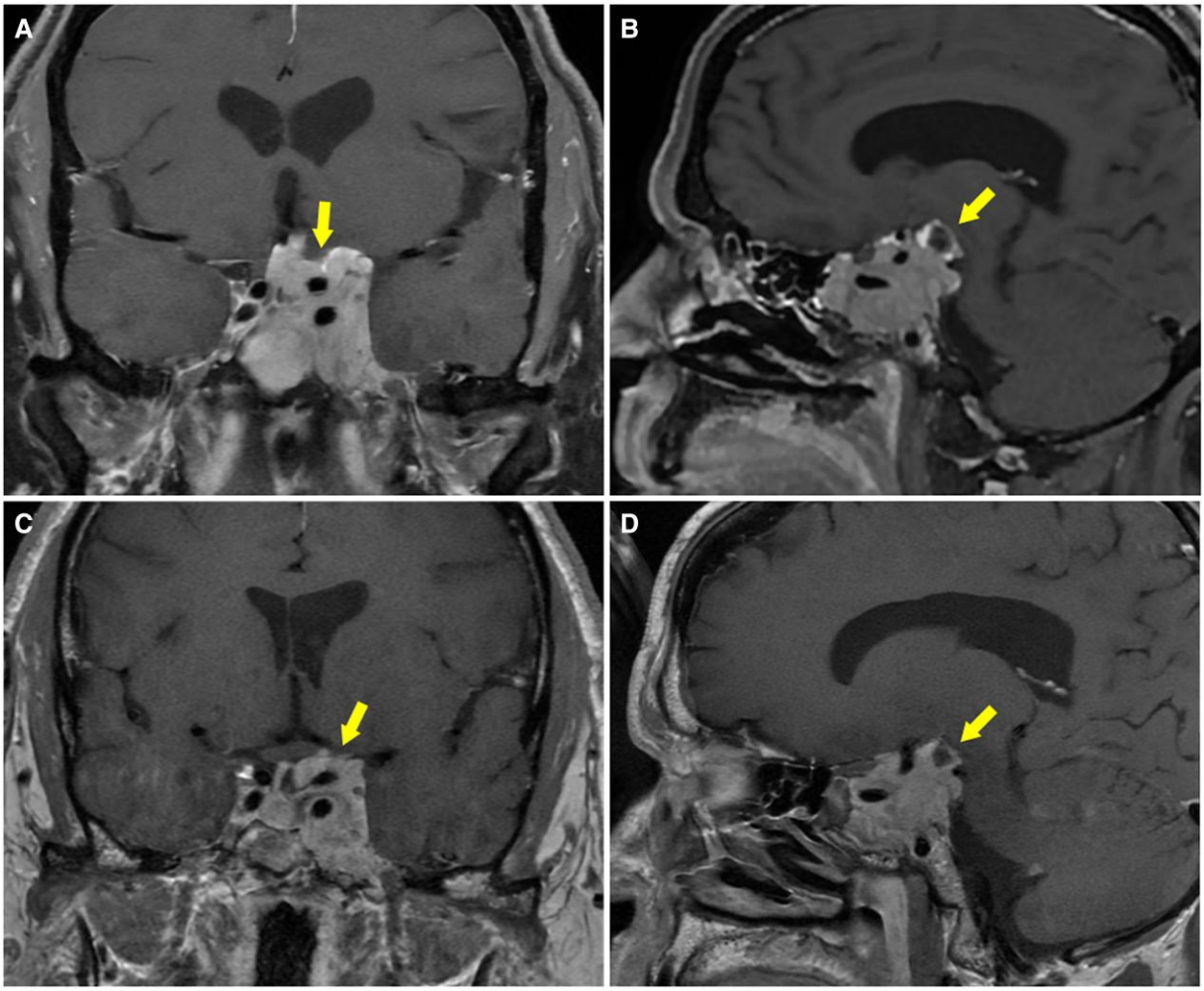

Figure 1. Gadolinium-enhanced T1-weighted MRI of the sella. (A) In the coronal view, a large sellar mass measuring up to 4.2 cm was observed invading the left cavernous sinus and encasing the left internal carotid artery (arrow), with superior displacement of the optic chiasm. (B) In the sagittal view, tumoral cyst was visualized within the suprasellar cistern (arrow). (C, D) Following subtotal transsphenoidal resection, the tumor measured up to 2.6 cm with similar encasement of the left internal carotid artery (coronal, arrow) and decrease in size of the tumoral cyst (sagittal, arrow).

Table 1. Serum prolactin and catecholamine levels before and after paraganglioma and pituitary surgery

Hormone	Reference range	Baseline lab values	Labs after paraganglioma resection	Labs after pituitary surgery[a]	Most recent labs[b]
Prolactin, serum	2-18 ng/mL (2-18 µg/L)	**130.9 ng/mL (130.9 µg/L)**	**877.8 ng/mL (877.8 µg/L)**	**22.2 ng/mL[c] (22.2 µg/L)**	2.9 ng/mL[c] (2.9 µg/L)
Dopamine, plasma	<36.7 pg/mL (<240 pmol/L)	**2531 pg/mL (16 522 pmol/L)**	23.2 pg/mL[d] (152 pmol/L)	29.7 pg/mL[d] (194 pmol/L)	<19 pg/mL[d] (<124 pmol/L)
Epinephrine, plasma	</= 60 pg/mL (</= 330 pmol/L)	**68 pg/mL (370.9 pmol/L)**	27.8 pg/mL[d] (152 pmol/L)	38.6 pg/mL[d] (211 pmol/L)	33.4 pg/mL[d] (183 pmol/L)
Norepinephrine, plasma	177.5-811 pg/mL (1050-4800 pmol/L)	**851 pg/mL (5032 pmol/L)**	**864 pg/mL[d] (5117 pmol/L)**	**858 pg/mL[d] (5081 pmol/L)**	400.3 pg/mL[d] (2369 pmol/L)
Free metanephrine, plasma	</= 57 pg/mL (</= 289 pmol/L)	<25 pg/mL (<126.8 pmol/L)	19.7 pg/mL[c] (<100 pmol/L)	29.5 pg/mL[c] (150 pmol/L)	31.5 pg/mL[c] (160 pmol/L)
Free normetanephrine, plasma	</= 148 pg/mL (</= 808 pmol/L)	144 pg/mL (786.2 pmol/L)	**238 pg/mL (1300 pmol/L)**	**194 pg/mL[c] (1060 pmol/L)**	120.8 pg/mL[c] (660 pmol/L)

Abnormal values are shown in bold font.

[a]5 months after paraganglioma resection; 2 months after pituitary surgery.

[b]8 months after paraganglioma resection; 5 months after pituitary surgery.

[c]On cabergoline.

[d]Labs were measured under SI units and converted to pg/mL conventional units for manuscript data presentation.

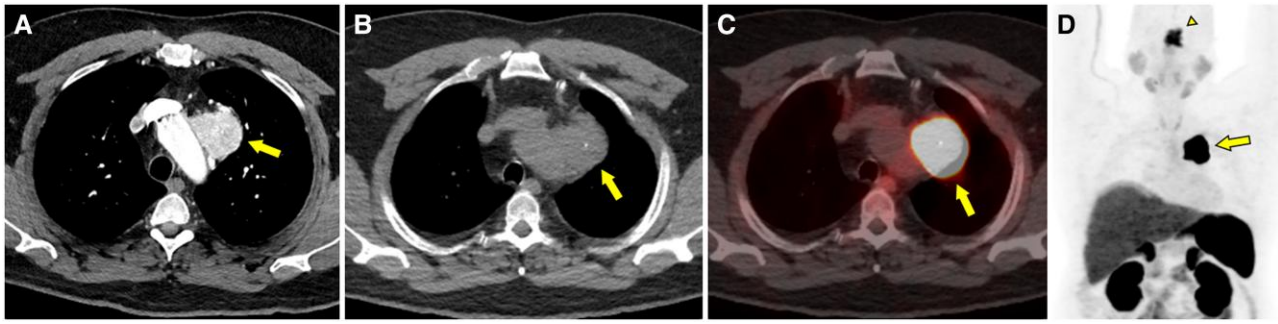

Figure 2. Paraganglioma imaging studies. (A) Chest CT with intravenous contrast revealed a heterogeneously enhancing left anterior mediastinal mass (arrow) measuring 4.7 cm with central punctate calcification. (B, C) The mediastinal mass (arrow) exhibited intense uptake with ^{68}Ga-DOTATATE PET/CT. (D) In the maximum intensity projection, increased DOTATATE activity was observed in both the mediastinal (arrow) and sellar (arrowhead) masses.

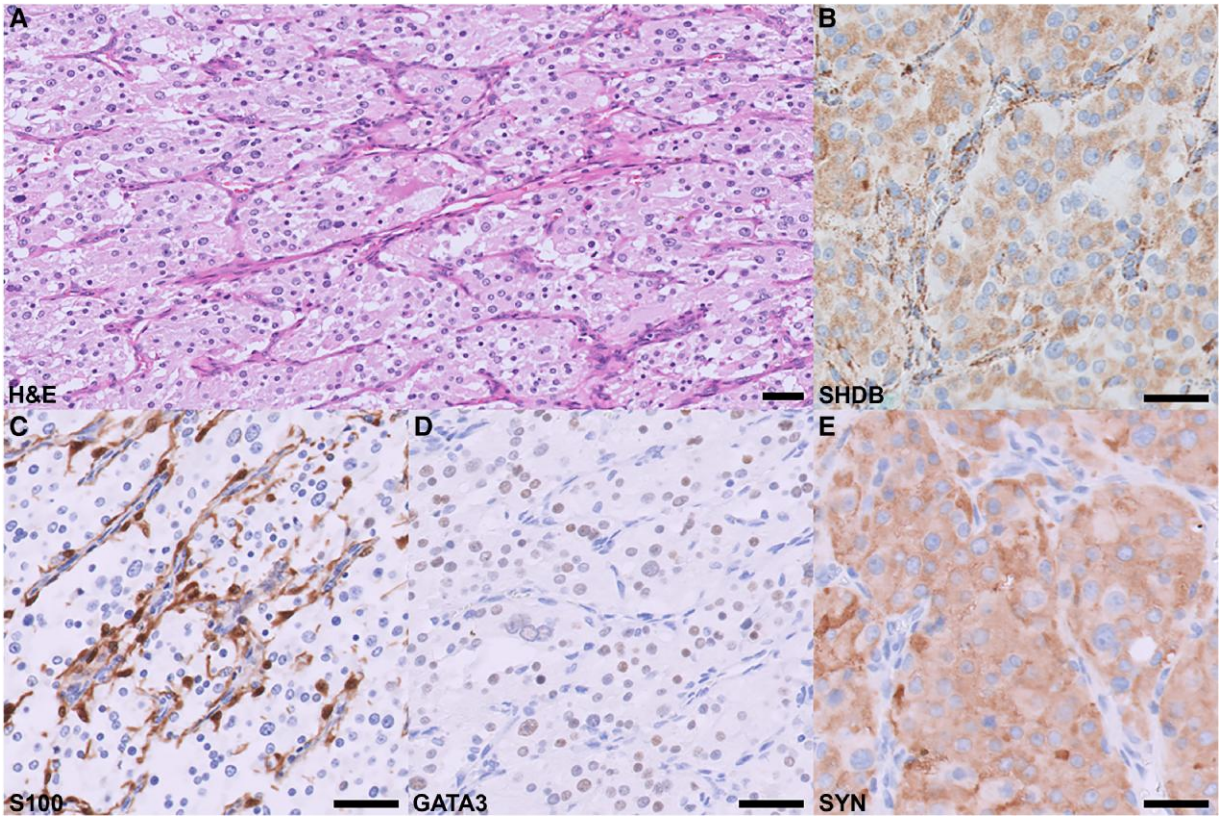

Figure 3. Paraganglioma pathology. (A) Hematoxylin and eosin (H&E)–stained section shows a proliferation of epithelioid cells arranged in a lobulated pattern bounded by sustentacular cells. By immunohistochemistry, the tumor cells have granular cytoplasmic staining for SHDB (B). S100 highlights the sustentacular cells (C). Tumor cells are also positive for GATA3 (D) and synaptophysin (SYN, E). Scale bar represents 50 μm.

secretion from the paraganglioma exerted tonic inhibition on prolactin secretion from the pituitary adenoma. Removal of the paraganglioma unmasked prolactin hypersecretion (Fig. 5). To our knowledge, this is the first time that these hormonal interactions between a dopamine-secreting paraganglioma and prolactinoma have been described in the literature. Of note, a similar transient rise in prolactin following the removal of dopamine excess can occur even without the presence of prolactinoma (ie, dopamine "withdrawal") [5]. However, this is a less probable cause in our case due to the very short half-lives of dopamine (<5 minutes) and prolactin (25-50 minutes) and discovery of severe hyperprolactinemia weeks out from paraganglioma surgery.

Interestingly, his pituitary adenoma stained positive for PIT1 but negative for prolactin, likely representing an immature PIT1-lineage tumor according to the 2022 WHO classification of pituitary tumors [6]. Immature PIT1-lineage pituitary adenomas are less differentiated and may exhibit variable hormone staining and secretion [6, 7]. Tumors are usually larger and display more aggressive features, such as higher rates of invasion into parasellar compartments and residual disease or recurrence following initial surgery [6, 8, 9]. Significant hyperprolactinemia (>150 ng/mL [150 μg/L]) seems to be rare among both mature and immature PIT1 lineage pituitary adenomas [7, 10], so our case appears more in line with a clinically functional prolactinoma despite negative

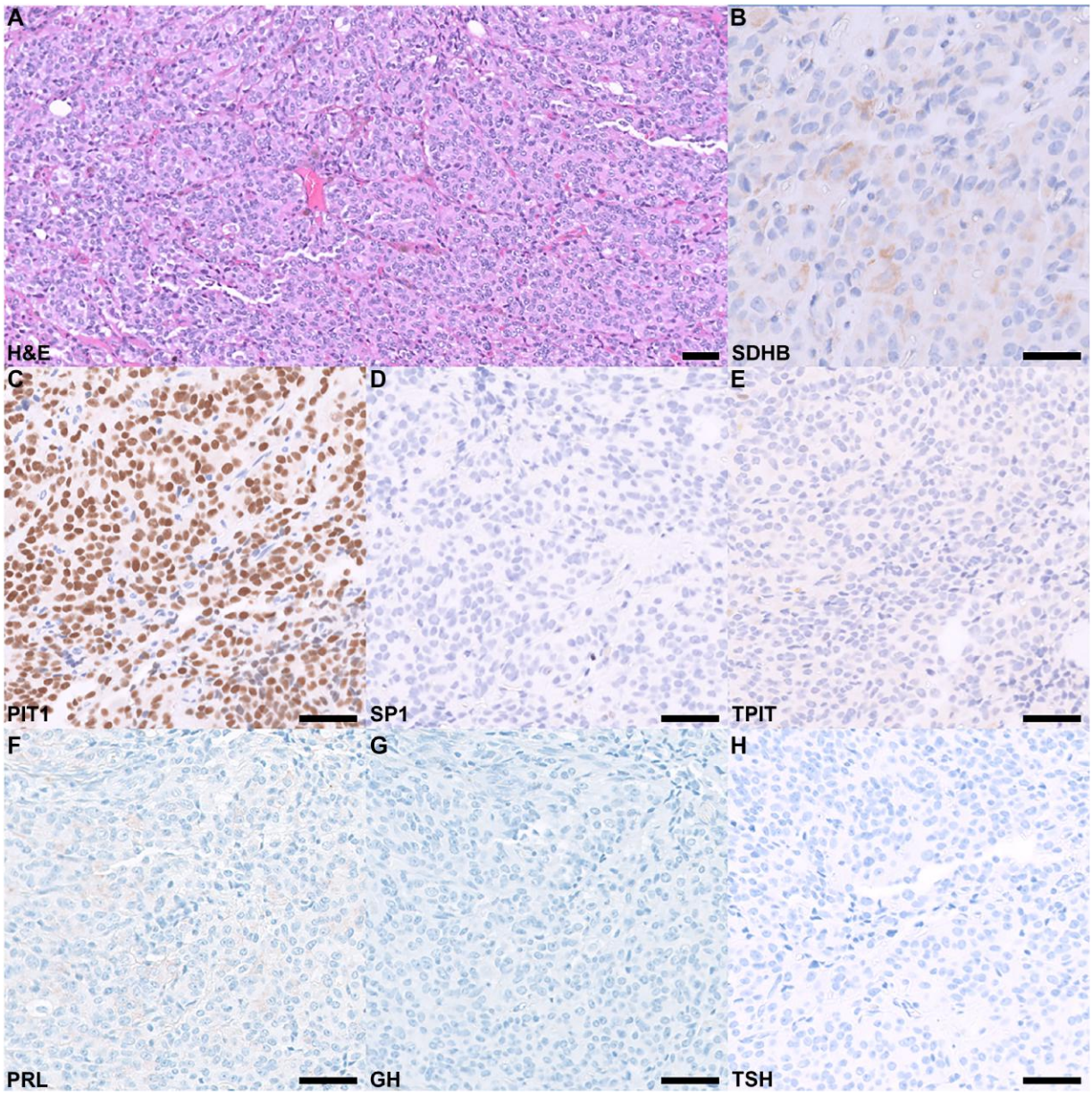

Figure 4. Pituitary pathology. (A) Hematoxylin and eosin (H&E)–stained sections show a proliferation of epithelioid cells arranged in expanded nests and sheets. By immunohistochemistry, the tumor cells have a weak granular cytoplasmic staining for SHDB (B). The tumor cells are positive for transcription factor PIT1 (C) and negative for transcription factors SF1 (D) and TPIT (E). The tumor is also negative for prolactin (PRL, F), growth hormone (GH, G), and thyroid-stimulating hormone (TSH, H). Scale bar represents 50 µm.

prolactin staining. The prolactin being less than 1000 ng/mL [1000 µg/L] indicates that his mass is still likely less functional than a fully differentiated prolactinoma of similar size.

Dopamine-secreting paragangliomas are also rare and can escape clinical and biochemical attention. Patients often present with normal blood pressure or even orthostatic hypotension without classic symptoms of catecholamine excess, and such paragangliomas are associated with a high rate of metastasis [11-14]. Although all patients with a hormonally functional PPGL are recommended to undergo preoperative alpha blockade, such therapy is less supported by clinical evidence in patients with purely dopaminergic PPGL [15]. Systemic dopamine evokes selective vasodilation of vascular beds and increased cardiac output, and at high levels, increased systemic vascular resistance due to alpha-adrenergic stimulation. Cardiovascular collapse after resection of dopamine-secreting PPGLs has been described [16].

Paragangliomas are often hereditary with over a dozen known susceptibility genes. The most frequently mutated susceptibility gene is *SDHB*, which encodes subunit B of SDH [17, 18]. While most prolactinomas occur sporadically, they have also been described in the context of germline pathogenic variants responsible for hereditary neoplasia syndromes [19]. Sporadic and familial pituitary adenomas have been reported in SDH-deficient PPGL patients, suggesting a rare syndromic relationship referred to as the 3P association (3PAs; pituitary adenoma, paraganglioma, and/or pheochromocytoma) [20].

However, our findings did not suggest that the patient's germline heterozygous variant *SDHC* c.155T>C is pathogenic. This sequence change replaces leucine with proline at codon 52

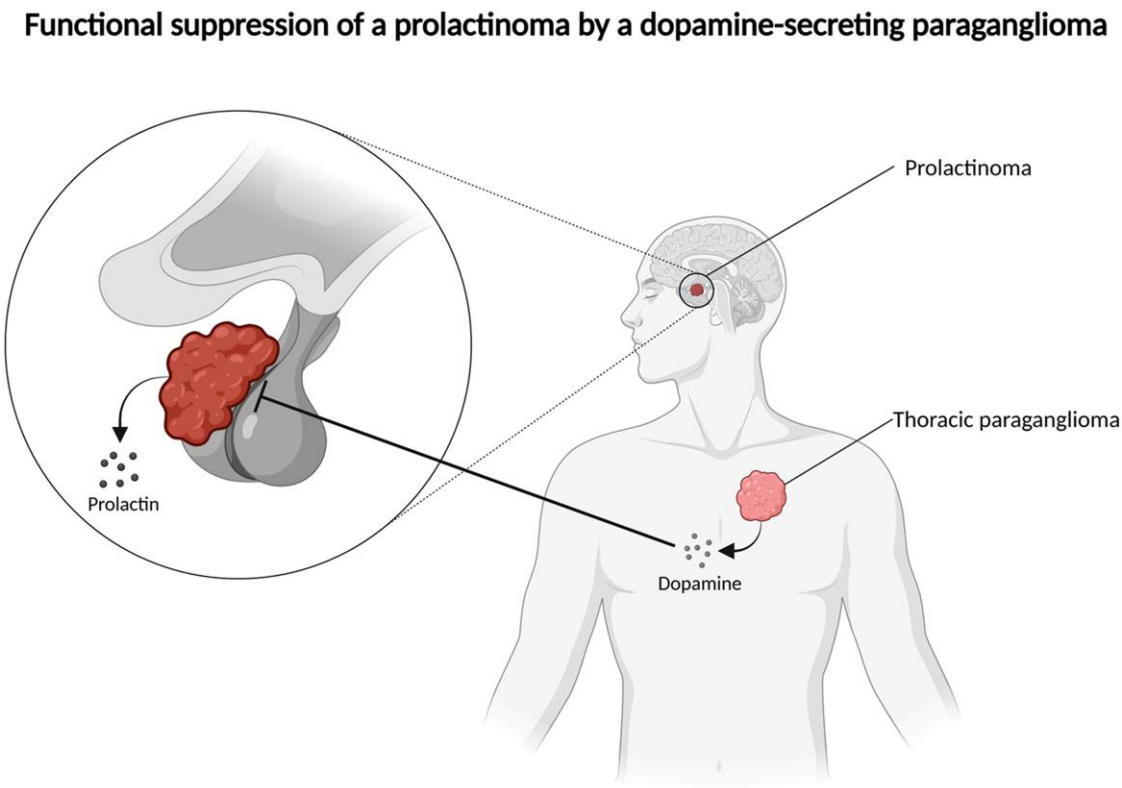

Figure 5. Proposed mechanism of functional suppression of a prolactinoma by a dopamine-secreting paraganglioma. Dopamine is secreted from the paraganglioma into the systemic circulation, leading to increased dopamine concentration in the hypophyseal portal system. Increased dopamine binding to the dopamine D2 receptor inhibits prolactin secretion from the prolactinoma. Removal of the source of excess dopamine via paraganglioma resection results in disinhibition of prolactin secretion. The prolactin remains elevated from continued secretion from the prolactinoma. Functional dopamine withdrawal may also cause transient (<60 minutes) hyperprolactinemia in the absence of prolactinoma. Created in BioRender.

(p.Leu52Pro) of the SDHC protein, an integral membrane protein that anchors SDHB to the inner mitochondrial membrane. Although Invitae modeling predicted that the Leu52Pro missense mutation would disrupt SDHC protein function, further examination revealed Leu52 to be located within an unstructured region where proline substitution is likely to be tolerated. Since SDHB staining is lost in 90% to 100% of pathogenic variants of any SDH subunit gene (including SDHC), SDHB immunohistochemistry may help predict the pathogenicity of SDH variants [3, 21, 22]. Considering the intact SDHB staining in this case, it is unlikely that *SDHC* c.155T>C increases risk for PPGLs, and thus, it remains a VUS. This is the first report to identify the germline *SDHC* c.155T>C variant which is not reported in ClinVar or gnomAD, large databases of human genetic variants.

Next steps for the patient include close biochemical and radiographic surveillance of his prolactinoma and paraganglioma. While his prolactin has responded well to cabergoline, further reduction of tumor size is yet undetermined. Other medical options to reduce tumor size may include somatostatin receptor ligands, although there is mixed evidence of effectiveness of these therapies [23-25]. Radiation and/or further surgical debulking may be reconsidered if there are signs of growth.

Learning Points

- Endogenous dopamine production from hyperfunctioning PPGLs can suppress pituitary prolactin secretion.
- Immature PIT1-lineage pituitary adenomas are less differentiated, possess variable hormone immunostaining and secretion, and tend to be relatively larger and more aggressive.
- Dopamine-secreting PPGLs may be underrecognized due to frequent lack of symptoms, and management is often complicated by unpredictable hemodynamic events.
- Patients with paraganglioma and pituitary adenoma should be tested for genetic pathogenic variants that may have clinical implications on treatment and surveillance.

Contributors

All authors made individual contributions to authorship. T.F.: manuscript and tables preparation and submission. L.N.: preparation of radiology images and figures. L.N. and J.P.A.: genetic testing and counseling. K.L.B.: histopathology section and preparation of histology images. F.M.: management of preoperative alpha blockade and anesthesia during patient's surgeries. J.J.C.: diagnosis and management of the patient; manuscript preparation. All authors edited, reviewed, and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

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

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