

Case Report of a Prolactinoma in a Patient With a Novel *MAX* Mutation and Bilateral Pheochromocytomas

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Pheochromocytomas are neuroendocrine tumors that can arise sporadically or be inherited as a familial disease, and they may occur in isolation or as part of a multitumor syndrome. Familial disease typically presents in younger patients with a higher risk of multifocality. Recently, the tumor suppressor MYC-associated factor X (*MAX*) gene has been implicated as a cause of familial isolated pheochromocytoma and paraganglioma. We describe a patient with a pituitary prolactinoma and bilateral pheochromocytomas who tested positive for a germline *MAX* mutation. Interestingly, the patient also had mild primary hyperparathyroidism that resolved upon resection of the pheochromocytomas despite the absence of parathyroid hormone staining in the tumors. To our knowledge, this case is the first report of prolactinoma in a patient with a *MAX* mutation, which suggests the possibility of germline *MAX* mutations also contributing to the development of prolactinomas.

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Pheochromocytomas are rare tumors derived from neural crest cells in the adrenal medulla. Tumors overproduce catecholamines, leading to symptoms such as hypertension, palpitations, perspiration, headaches, pallor, and tremors. Studies have revealed that up to 20% to 40% of pheochromocytomas are familial [1–3].

Familial pheochromocytomas can be associated with genetic syndromes such as multiple endocrine neoplasia type 2 (*RET* proto-oncogene mutation), von Hippel–Lindau disease (*VHL* mutation), and neurofibromatosis type 1 (*NF1* mutation), but they may also present in isolation, as in the case of succinate dehydrogenase complex (*SDH A, B, C, D,* and *AF2*), and transmembrane protein 127 (*TMEM127*) mutations [4]. Comino-Méndez *et al.* [5] recently identified mutations in the tumor suppressor MYC-associated factor X gene (*MAX*) as a cause of hereditary pheochromocytoma. They examined 62 patients with pheochromocytomas and detected unique *MAX* mutations in eight families, totaling 12 affected patients.

Abbreviations: CT, computed tomography; *MAX*, MYC-associated factor X; *MEN1*, menin 1; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PTH, parathyroid hormone; *SDH*, succinate dehydrogenase complex; *TMEM127*, transmembrane protein 127; *VHL*, von Hippel–Lindau disease.

An investigation of 1694 pheochromocytoma/paraganglioma patients without mutations in *RET*, *VHL*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* identified germline *MAX* mutations in 23 patients and somatic *MAX* mutations in 4 of 245 tumors [6]. These *MAX* mutation carriers included patients with bilateral pheochromocytomas, as well as multiple pheochromocytomas within the same gland [6]. Another study of 153 pheochromocytoma/paraganglioma cases in patients presenting under age <40 years with multiple tumors identified genetic mutations in 73 patients (47%), one of which was a *MAX* mutation [7]. Germline *MAX* mutations have been associated with pheochromocytoma, paraganglioma, and renal oncocytoma, whereas somatic *MAX* mutations have been linked to formation of other tumors, including endometrioid carcinoma, colon carcinoma, and small-cell lung carcinoma.

Benign pituitary adenomas can be sporadic, familial, or part of a genetic syndrome. The most common inherited forms of pituitary adenoma are multiple endocrine neoplasia type 1 [menin 1 (*MEN1*), cyclin-dependent kinase inhibitor 1B (*CDKN1B*) genes], familial isolated pituitary adenoma [aryl hydrocarbon receptor–interacting protein (*AIP*) gene], and Carney complex [protein kinase cyclic adenosine monophosphate–dependent type 1 regulatory subunit α (*PRKARIA*) gene] [8]. Pituitary adenomas and pheochromocytomas/paragangliomas are rarely part of the same syndrome. A recent report of 39 patients with pheochromocytoma/paraganglioma along with a pituitary adenoma detected germline mutations in *SDHB/C/D*, *VHL*, and *MEN1* but failed to identify any *MAX* mutations [9]. We describe a patient who presented with a pituitary prolactinoma, an endocrine disease not previously associated with *MAX* mutations, who was found to have bilateral pheochromocytomas and a germline *MAX* mutation.

1. Patient and Methods

A 49-year-old female presented with a headache and nausea and was found to have a 1.9-cm sellar mass on magnetic resonance imaging (MRI) (Fig. 1). She had been amenorrheic since age 35. Prolactin was markedly elevated at 1299 ng/mL (normal, 3.34 to 26.72 ng/mL). There was no reported evidence of pituitary hormone cosecretion or deficiency other than central hypogonadism.

On cabergoline 0.5 mg by mouth twice per week, the prolactin level and tumor size decreased (Fig. 1), but her symptoms persisted. Four months later, she presented to our center. At this time, the prolactin had decreased to 31.2 ng/mL (normal, 0.0 to 20.0 ng/mL) (see Table 1 for laboratory values). She reported 8 months of palpitations, headaches, and pallor. Biochemical testing for pheochromocytoma revealed plasma normetanephrine levels 20-fold above the upper limit of normal, with minimal elevation of metanephrine levels (Table 1).

Laboratory values were also significant for a low free T4 of 0.7 ng/dL (normal, 0.9 to 1.8 ng/dL), a follicle-stimulating hormone level of 12.9 U/L (normal for postmenopausal women, 18.0 to 153.0 U/L), a luteinizing hormone level of 12.4 U/L (normal for postmenopausal women, 16.0 to 64.0 U/L), an estradiol level of <20 pg/mL (normal for postmenopausal women, <59 pg/mL), a human chorionic gonadotropin level of <6 IU/L (<6 indicates nonpregnant), an IGF-I level of 97 ng/mL (normal, 52 to 328 ng/mL; z score of 0.8), and a cortisol level of 25.2 μ g/dL (45 min after 250 μ g of intramuscular cosyntropin; normal > 18 μ g/dL). She had a sodium level of 144 mmol/L (normal, 135 to 145 mmol/L), a potassium level of 4.5 mmol/L (normal, 3.4 to 4.8 mmol/L), and a creatinine level of 1.05 mg/dL (normal, 0.60 to 1.50 mg/dL). Additionally, she had mildly elevated calcium with an inappropriate parathyroid hormone (PTH) level in the high normal range, normal albumin, mildly low vitamin D, and elevated 24-hour urine calcium, consistent with primary hyperparathyroidism (Table 1). She was started on levothyroxine for central hypothyroidism. Adrenal protocol computed tomography (CT) showed 1.7-cm and 1.3-cm left adrenal nodules and a 2.1-cm right adrenal nodule (Fig. 1). A metaiodobenzylguanidine (MIBG) scan showed increased [¹²³I]MIBG uptake in the 1.3-cm superomedial left adrenal lesion suspicious for pheochromocytoma and no evidence of increased radiotracer uptake in the other adrenal lesions. An aldosterone, renin, 1 mg overnight dexamethasone suppression test and 24-hour urine-free cortisol were normal.

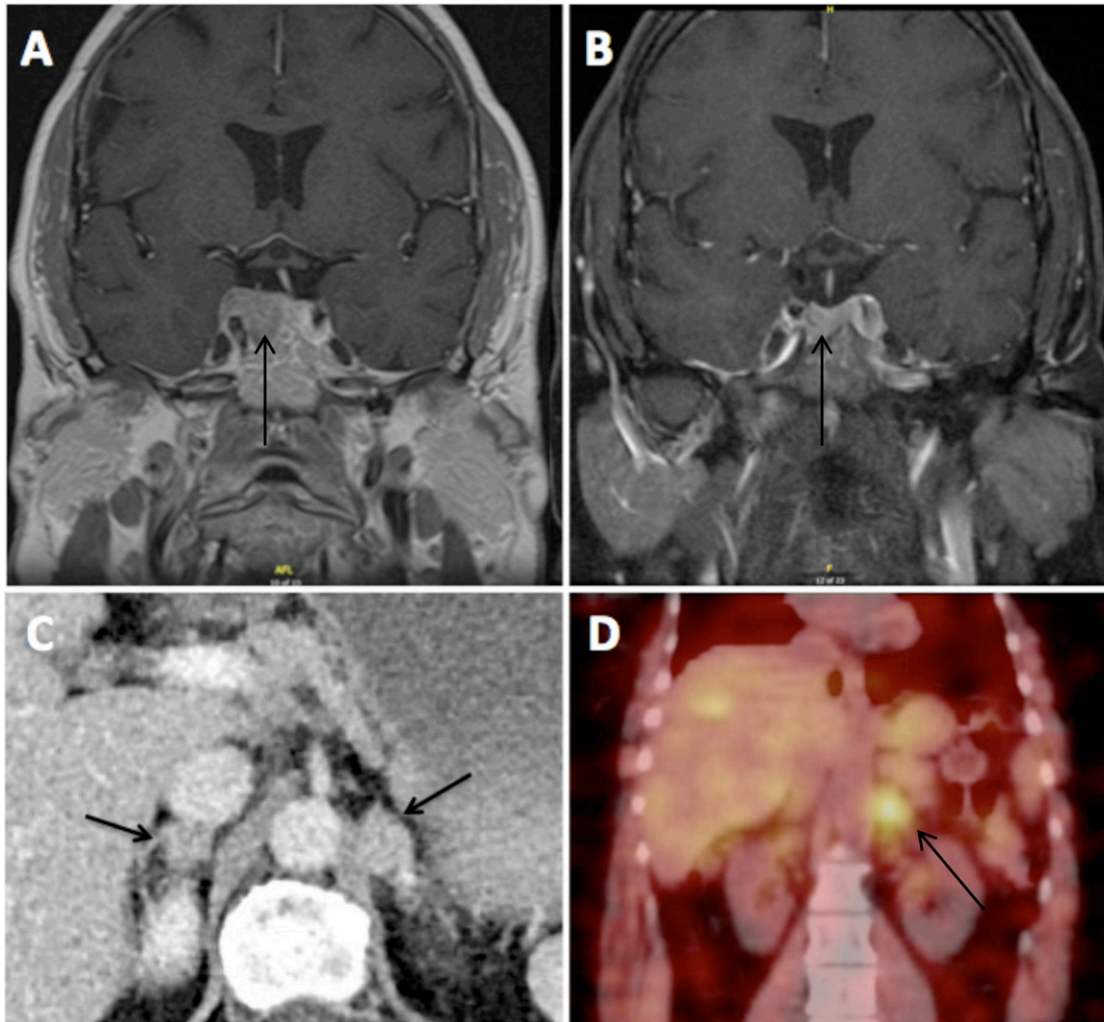


Figure 1. (A) Postcontrast pituitary protocol MRI on presentation demonstrating a 1.9-cm sellar mass, with a possible hemorrhagic component, extending into the cavernous sinus and abutting the right optic nerve. (B) Postcontrast pituitary protocol MRI while on treatment with cabergoline showed decreased tissue in the right sellar and suprasellar space, consistent with a response to therapy. (C) Adrenal protocol CT scan identified three nodules: two left nodules measuring 1.7×1.7 cm (not shown in figure) and 1.3×1.3 cm (arrow), and a right nodule (arrow) measuring 2.0×1.3 cm. All of the lesions were >10 Hounsfield units on noncontrast imaging, enhanced to values <100 Hounsfield units on early postcontrast images, and did not show abundant washout on 10 minute delayed images; therefore, they did not meet CT criteria for adenoma and were not hypervascular to suggest pheochromocytomas. They were thus considered indeterminate on imaging. (D) Whole-body MIBG scan showed increased $[^{123}\text{I}]\text{MIBG}$ uptake in the 1.3-cm superomedial left adrenal lesion suspicious for pheochromocytoma without increased uptake in the inferolateral left or right lesions.

Given the lack of family history, the high frequency of benign adrenal adenomas, and the desire to preserve endogenous adrenal function, a unilateral adrenalectomy was elected. A laparoscopic left adrenalectomy was performed following perioperative alpha and beta blockade. Pathologists diagnosed both lesions as pheochromocytomas (Fig. 2), and routine SDHB immunostaining showed low positive expression of SDHB protein, indicating a lack of mutated SDHA or SDHB. Immunohistochemistry for the MAX protein revealed positive nuclear staining in a control pheochromocytoma, as well as in the patient's adrenal cortex, endothelium, and lymphocytes; however, the patient's pheochromocytoma cells were negative for the MAX protein (Fig. 2). Postoperatively, her nausea persisted, but the sweats,

Table 1. Laboratory Values at Baseline and After Left and Right Adrenalectomies

	Presentation to Our Clinic (on Cabergoline 0.5 mg Twice per Week)	Repeat	After Left Adrenalectomy	After Right Adrenalectomy
Prolactin, ng/mL	31.2 (3.34–25.72)			45.5 (3.34–25.72)
Plasma-free normetanephrine, nmol/L	25 (<0.9)		5.4 (repeat 5.6) (<0.9)	0.69 (<0.9)
Plasma-free metanephrine, nmol/L	0.74 (<0.5)		<0.2 (<0.5)	<0.20 (<0.5)
24-h urine norepinephrine, µg/d	1076 (15–100)		507 (15–100)	
24-h urine epinephrine, µg/d	26 (2–24)		14 (2–24)	
24-h urine dopamine, µg/d	444 (52–480)	16 (<21)		
24-h urine normetanephrine, µg/d	4014 (88–649)	1363 pg/mL (<148)	2381 (88–649)	230 (122–676)
24-h urine metanephrine, µg/d	363 (58–203)	90 pg/mL (<58)	167 (58–203)	<5 (n/a, below reference range)
24-h urine total metanephrines, µg/d	4377 (182–739)	1453 pg/mL (<205)	2548 (182–739)	230 (244–832)
PTH, pg/mL	53 (10–60)	75 (10–60)		31 (10–60)
Calcium, mg/dL	11.1 (8.5–10.5)	10.2 (8.5–10.5)	9.7 (8.5–10.5)	9.8 (8.5–10.5)
Vitamin D, ng/mL	24 (>32)			26 (>32)
24-h urine calcium, mg/d	454 (100–300)			

Abbreviation: n/a, not available.

palpitations, headache, and pallor resolved and she remained normotensive off all antihypertensive medications. Her menstrual cycles returned. However, plasma normetanephrine levels remained sixfold higher than the upper limit of normal. A MIBG scan and CT of the neck and chest were negative.

MRI of the remaining adrenal gland and abdomen showed features of pheochromocytoma in the right adrenal nodule without evidence of metastatic disease to the liver (Fig. 1). A laparoscopic right adrenalectomy was performed and the pathology was consistent with a pheochromocytoma (Fig. 2). Postoperatively, she was maintained on glucocorticoid and mineralocorticoid replacement. Laboratories revealed no biochemical evidence of pheochromocytoma. Calcium and PTH levels decreased to the midnormal range. Immunohistochemistry for PTH was therefore performed on the adrenal lesions, but was negative.

Her family history was not notable for pituitary or neuroendocrine tumors. Five of the 10 children in her family had kidney stones but were otherwise healthy. A genetics work-up revealed no mutations in the *MEN1*, *VHL*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, or *TMEM127* genes. Further analysis revealed a likely pathogenic *MAX* mutation c.296-1G>T (NM_002382), which has not been previously described. The variant was not present in the Genome Aggregation Database, which includes >130,000 genomes. The mutation occurred one nucleotide prior to the coding region of exon 5, a position that is conserved in vertebrate species. The alteration disrupts a canonical splice acceptor site, which is thought to eliminate transcription of the gene or induce nonsense-mediated decay of a mutated transcript. (AmbryGenetics Test Report, Aliso Viejo, CA). Additionally, the *RET* gene (NM_020630) had an American College of Medical Genetics and Genomics category 6 alteration, p.S836S (c.2508C>T), which is a silent mutation that conserves the RET protein sequence. Whereas some studies have implicated this silent *RET* mutation in increasing the chance of developing sporadic medullary thyroid cancer, others showed no increase in risk of thyroid cancer [10], pheochromocytomas, or pituitary adenomas [11].

Sixteen months since the biochemical cure of her pheochromocytomas, the patient continues to have fatigue and nausea. Symptoms did not improve with adjustments to her corticosteroid replacement or a trial off of cabergoline. Biochemical evaluation has been repeatedly negative for recurrent pheochromocytoma/paraganglioma. CT and/or MRI

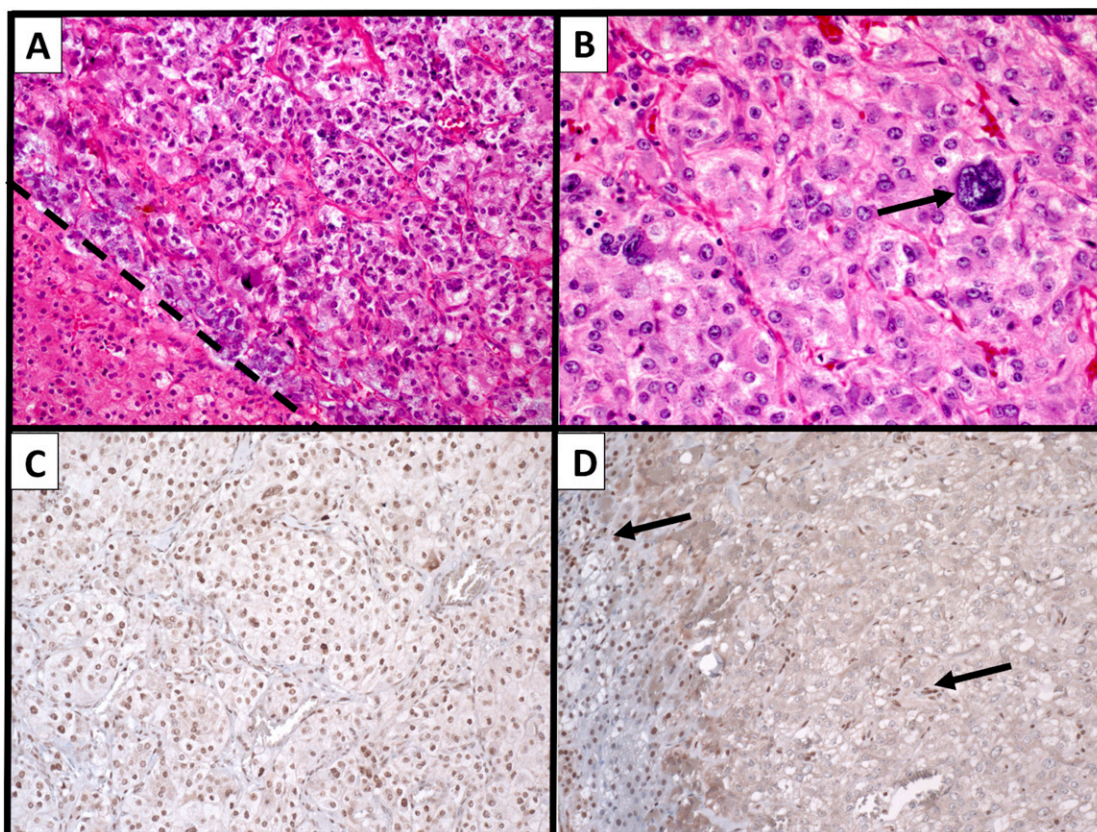


Figure 2. (A) The right adrenal gland shows nests of round blue cells (“zellballen”) of pheochromocytoma overlying adjacent adrenal cortex below (dashed line; H&E; original magnification, $\times 200$). (B) The left adrenal gland shows the zellballen of the pheochromocytoma at high power (H&E; original magnification, $\times 400$) with endocrine nuclear atypia (arrow) (one of two lesions on the left). Immunohistochemistry was performed for the MAX protein. (C) A control pheochromocytoma (original magnification, $\times 200$) showed positive staining for MAX in the nuclei of pheochromocytoma cells. (D) The patient’s pheochromocytoma (original magnification, $\times 200$) showed positive staining for the MAX protein in the adrenal cortex, endothelium, and lymphocytes (arrows), but MAX staining was absent in the patient’s pheochromocytoma cells.

imaging of the neck, chest, and abdomen, and whole-body MIBG scans were negative for additional pathology. A work-up for nausea by gastroenterology is ongoing. She will be followed closely with continued surveillance for recurrence of pheochromocytoma, paraganglioma, or hyperparathyroidism.

2. Discussion

We describe a patient who presented with a prolactinoma and was found to have bilateral pheochromocytomas and a novel *MAX* mutation. Although *MAX* mutations have been demonstrated to cause familial pheochromocytomas, to our knowledge, this is the first report of a pituitary adenoma in a patient with a *MAX* mutation. Immunohistochemistry revealing loss of the MAX protein in the patient’s pheochromocytoma cells suggests that this novel mutation of *MAX* was responsible for tumorigenesis. Loss of heterozygosity studies would have been useful in confirming the loss of the normal *MAX* allele at the genetic level. Tissue from the pituitary tumor is not available for analysis; therefore, it is impossible to directly implicate a *MAX* mutation as a causative event for tumor formation. The pituitary adenoma could be a coincidental finding in this patient with a germline *MAX* mutation.

MAX has been shown to behave as a classical tumor suppressor gene, with loss of heterozygosity of the normal allele in tumors carrying pathogenic mutations [5, 7]. The *MAX* protein interacts with the *MYC* proto-oncogene and the *MAX* dimerization protein 1 (*MXD1*) family of proteins. *MAX* mutations appear to cause pheochromocytoma by failing to control *MYC* signals for cellular proliferation [12].

Consistent with findings from other pheochromocytomas harboring *MAX* mutations, our patient's tumor secreted normetanephrine in a greater proportion than metanephrine [5–7]. An interesting aspect of this case was the inconsistent uptake of [¹²³I]MIBG in the adrenal lesions. The absence of [¹²³I]MIBG positivity could reflect the varying degrees to which pheochromocytomas, particularly dedifferentiated tumors, accumulate MIBG [13].

On presentation, the patient had mild primary hyperparathyroidism, which normalized after removal of the pheochromocytomas. Rarely, pheochromocytoma can cause hypercalcemia, which is thought to be mediated either by a primary process of the parathyroid glands (associated with multiple endocrine neoplasia) or directly from the pheochromocytoma, likely due to secretion of parathyroid-related protein [14]. Our patient's hypercalcemia improved after adrenalectomy, without intervention to the parathyroid glands. Hypercalcemia mediated by parathyroid-related protein secreted from the pheochromocytoma would be expected to suppress PTH levels, but this was not the case in our patient. Therefore, we hypothesized that the pheochromocytoma might secrete PTH ectopically, but immunohistochemistry was negative for PTH; thus, the source of primary hyperparathyroidism remains unclear.

This case is important in that, to our knowledge, it is the first report of a pituitary tumor, specifically a prolactinoma, in combination with pheochromocytomas in a patient with a germline *MAX* mutation. It raises the question of whether *MAX* mutations could cause a syndromic disease involving pituitary tumors in addition to pheochromocytomas/paragangliomas. Because *MAX* mutations are rare events, observations from case reports are important to identify potentially related clinical sequelae.

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