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Case Report

Surgical Remission of Diabetes in a Patient With Mutation of *RET* Proto-Oncogene

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ABSTRACT

Objective: In pheochromocytomas, accelerated catecholamine production can cause secondary diabetes. The gene responsible for multiple endocrine neoplasia type 2 (MEN2)-related pheochromocytomas is the *RET* proto-oncogene. The objective of this report is to describe a unique case of surgical remission of misdiagnosed type 2 diabetes mellitus (T2DM) in a woman with bilateral pheochromocytoma and *RET* proto-oncogene mutation.

Methods: Clinical examination, urinary metanephrine level, triple-phase abdominal computed tomography (CT) with adrenal protocol, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with CT, surgical pathology, and genetic testing were performed.

Results: A 46-year-old woman with a 5-year history of apparent T2DM complicated by neuropathy, without a contributory family history, presented with occasional headaches, weight loss, and abdominal pain. A 24-hour urinary metanephrine of 5 mg (reference range, 0.05-1 mg) was found. Abdominal CT showed bilateral adrenal masses with <60% washout. Positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with CT showed a left solid-cystic lesion with low metabolic activity and a right nodular lesion with a higher metabolic activity, which was conclusive of bilateral pheochromocytoma. The remission of diabetes was achieved 1 year after a bilateral adrenalectomy. In addition, a multinodular goiter was found, and a fine-needle aspiration biopsy confirmed that it was a medullary thyroid carcinoma. A heterozygous pathogenic variant of the *RET* proto-oncogene was found and MEN2A was confirmed.

Conclusion: This is the first report of a patient with a *RET* proto-oncogene mutation experiencing remission of diabetes after surgical resection of bilateral pheochromocytomas. Timely recognition and treatment of the underlying condition are important to potentially achieve diabetes remission and prevent its long-term complications.

Introduction

Multiple hormones participate in the physiologic regulation of blood glucose levels, and it is well known that their altered production may cause hyperglycemia. Particularly, hormones involved in insulin counterregulatory response, such as glucagon, catecholamines, cortisol, or growth hormone, have strong hyperglycemic action, and they may lead to secondary diabetes.[1]

Pheochromocytomas are rare neuroendocrine tumors, usually benign, and derived from the catecholamine-producing chromaffin cells of the adrenal medulla.[2] They have the strongest heritability of all endocrine tumors.[3] One-third of those tumors are believed to be caused by germline mutations.[2]. At least 12 pheochromocytoma-related genetic syndromes, 15 well-characterized driving genes, and potential disease-modifying genes have been identified.[4]

Abbreviations: CT, computed tomography; MEN2A, multiple endocrine neoplasia type 2A; T2DM, type 2 diabetes mellitus.

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Table 1
Pertinent Laboratory Investigations

Parameter	Reference range	Result
Hemoglobin, g/dL	13.5-17.5	12.7
White blood cell count, cells/mm^3	4500-11000	8280
Platelets count, cells/mm^3	150 000-400 000	248 000
Fasting serum glucose, mg/dL	80-130	174
Creatinine, mg/dL	0.6-1.2	0.39
Sodium, mEq/L	135-145	144
Potasium, mg/dL	3.5-5.0	4.4
Alanine aminotransferase, IU/L	<35	78
Aspartate aminotransferase, IU/L	<35	73
Alkaline phosphatase, IU/L	20-130	100
γ-Glutamyltranspeptidase, IU/L	9-64	81
Albumin, g/dL	3.5-5.5	3.9
Total bilirrubin, mg/dL	0.1-1.2	0.7
Glycated hemoglobin, % (mmol/mol)	<5.7 (34)	7 (53)
24-hour urinary metanephrines, mg	0.05-1	5
24-hour urinary normetanephrines, mg	0.08-0.4	0.3
Carcinoembryonic antigen, ng/mL	<10	71.54
Alpha fetoprotein, ng/mL	<8,1	3.2
Cancer antigen 19-9, IU/mL	<37	19.85
Calcitonin, pg/mL	0-11.5	>2000
Parathyroid hormone, pg/mL	10-65	15.3
Thryroid-stimulating hormone, IU/mL	0.40-4.20	0.34
Free thyroxine, ng/dL	0.8-1.5	1.13
Morning cortisol, μg/dL	6.7-22.6	22
Overnight cortisol after 1 mg of dexamethasone, μg/dL	<1.8	1.2
Aldosterone, ng/dL	2.94-16.1	3.1

Although pheochromocytomas can appear at any age, they are more common in the fourth or fifth decade of life, with a slight predilection in women (55.2%).[5–7]

We present the case of a patient with diabetes secondary to bilateral pheochromocytoma that remitted after surgical resection of the adrenals, emphasizing the importance of a proper diagnosis and treatment of diabetes secondary to endocrine disorders for preventing long-term complications.

Case Report

A 46-year-old, Peruvian woman was diagnosed with type 2 diabetes mellitus with overt neuropathy 5 years ago. Her regular treatment was metformin 850 mg three times daily with partial control of hyperglycemia. She did not have a history of hypertension, pre-eclampsia, or gestational diabetes and there was no family history of diabetes, endocrine-related tumors, or hypertension. Three years prior to admission, the patient experienced episodes of occasional oppressive, holocranial headaches. Over the following months, she complained of moderated epigastric pain that radiated to her left upper quadrant, associated with anorexia and weight loss of approximately 10 kg over 1 year. The symptoms persisted and she presented to the hospital where she was admitted.

On admission, physical examination revealed a cachectic patient with blood pressure, height, body weight, and body mass index of 120/70 mmHg, 150 cm, 45 kg, and 17.7 kg/m^2, respectively, a multinodular goiter, and distal sensory polyneuropathy of the lower limbs. Our endocrinology team was consulted because of her history of persistent hyperglycemia and multinodular goiter. Biochemical tests showed fasting hyperglycemia and mild elevated aminotransferases. The hormonal investigation demonstrated 24-hour urinary metanephrine of 5 mg (reference range, 0.05-1 mg). The patient's blood carcinoembryonic antigen level was elevated (Table 1).

A triple-phase abdominal computed tomography (CT) scan with adrenal protocol demonstrated a right adrenal 2.8 cm × 2 cm mass with definite and regular borders and a left adrenal 7.5 cm mass with extensive necrotic areas. Both lesions were contrast-enhanced with <60% washout (Fig. 1). A ^{123}Iodine-metaiodobenzylguanidine scan was not carried out because it was not available in our country. However, a positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with CT scan showed an extensive heterogeneous solid-cystic lesion, with low metabolic activity in the left adrenal gland and a hypodense nodular lesion with a higher metabolic activity in the right adrenal gland.

The clinical, hormonal, and imaging findings were conclusive of bilateral pheochromocytoma. The patient was given a 10-day course of the alpha-blocker terazosin 2.5 mg every 24 hours for 10 days. She required corrective doses of insulin only on the day before surgery. Subsequently, the patient underwent bilateral adrenalectomy complicated by a marked increase in intraoperative blood pressure caused by right-tumor manipulation. Gross examination of the surgical specimens is described in Figure 2. The pathologic examination of the adrenal tumors concluded that they were pheochromocytomas with positive markers for chromogranin and synaptophysin and a Ki67 index of <2%, all of which along with the absence of metastasis suggested a benign character.

Over the following days, a markedly increased calcitonin level of >2000 pg/mL (normal range, 0-11.5 pg/mL) was noted. Thyroid ultrasound showed neither extrathyroidal extension nor lymphadenopathy. A fine-needle aspiration biopsy of the thyroid was performed and revealed the proliferation of malignant cells with oval nuclei that were grouped into pseudofollicles and solid groups. As cytologic findings were indicative of medullary carcinoma, the patient underwent total thyroidectomy during which a 4 cm × 3 cm tumor in the right lobe and a 3 cm × 2 cm tumor in the left lobe were discovered. Pathologic examination of the surgical specimen and positive immunochemistry for calcitonin, chromogranin, and synaptophysin were conclusive of medullary thyroid cancer. The pheocromocytomas and medullary thyroid carcinoma were at stage T2N0M0 and stage T2N1bM0, respectively. A study to analyze a panel of 14 hereditary pheochromocytoma-paraganglioma genes was performed. The results were positive for the heterozygous pathogenic variant of the *RET* proto-oncogene Exon 11, denoted as RET:c.1901G>A (p. Cys 611Tyr). This pathogenic variant is

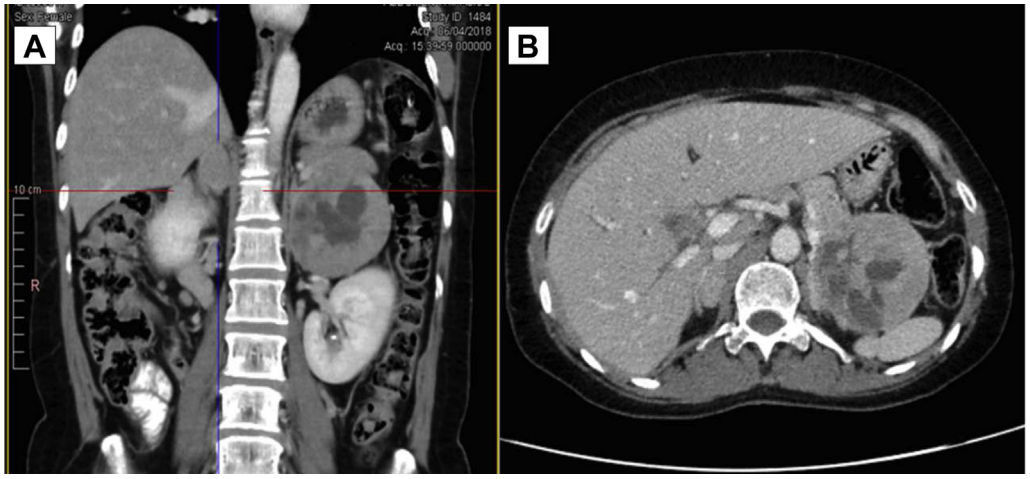

Fig. 1. Findings of abdominal triple-phase computed tomography scan with adrenal protocol. *A*, Coronal and *B*, axial views.

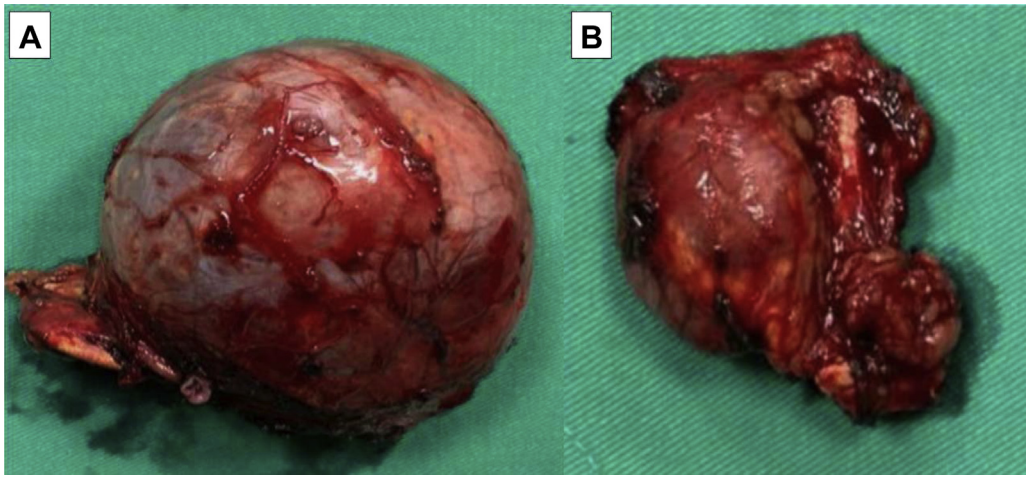

Fig. 2. Photograph of the removed adrenal tumors. *A*, A 10 cm × 8 cm large cystic-solid mass, multilobulated, thin walled, containing citrine fluid, and adhered to the anterior horn of the left adrenal gland, and *B*, a 4 x 4-cm solid-cystic tumor, thin walled, and adhered to the right adrenal gland.

associated with the autosomal dominant type 2A multiple endocrine neoplasia syndrome (MEN2A).

Complete remission of T2DM was achieved 1 year after surgery, evidenced by normoglycemia and glycosylated hemoglobin of 5.6% after antidiabetes medication withdrawal. The patient's residual hypothyroidism and adrenal insufficiency were treated with levothyroxine 100 μg/day and prednisone 7.5 mg/day (5 mg at 8:00 AM and 2.5 mg at 4:00 PM, respectively). The patient does not require mineralocorticoid therapy, is currently asymptomatic, and is attending our hospital's endocrinology clinic for follow-up.

Discussion

We describe the case of a patient with a history of T2DM in whom the diagnosis of MEN2A was confirmed by the clinical findings during her hospitalization and identification of a heterozygous germline *RET* pathogenic variant in genetic testing. The patient achieved remission of diabetes after surgical treatment of the adrenal glands. The documentation of this hereditary disease is important for a correct screening in relatives and to prevent complications such as diabetes mellitus secondary to a rare disease. Catecholamine-secreting tumors are rare neoplasms that occur in 0.1% to 0.2% of patients with hypertension and in 0.005% to 0.1% of the general population.[5] Most are sporadic, but 30% to 50% of patients have a tumor-related familial disorder, and usually have hereditary tumors at an earlier age.[6,8,9] In the present case, there was no contributory family history.

The principal familial disorders associated with adrenal pheochromocytoma are Von Hippel-Lindau syndrome, MEN2, and neurofibromatosis type 1. MEN2 is an autosomal dominant syndrome that affects 1 of every 30 000 to 35 000 individuals. It is caused by the activation of the *RET* proto-oncogene. MEN2A, which is present in 90% of all patients, carries almost 100% risk of medullary thyroid cancer and a 50% risk of pheochromocytoma. It also produces hyperparathyroidism (15% to 30% of cases). Many experts agree that performing genetic tests is crucial in patients who meet the clinical criteria for specific germline mutations. It is important to perform these tests in young adult patients, especially in bilateral cases, because of the relationship between those mutations and genetic syndromes.[10]

The prevalence of diabetes in patients with endocrinopathies varies from 33% to 50%.[1,11] However, diabetes secondary to endocrine disorders is very rare and constitutes less than 0.3% of diabetes cases worldwide.[12] The pathophysiology of impaired glucose tolerance in pheochromocytoma is multifactorial.

Table 2
Summary of Previously Reported Cases of Improvement or Remission of Diabetes After Surgical Resection of Pheochromocytoma

Author	Preoperative diabetes regimen	Postoperative diabetes regimen	Type of tumor	Genetic mutation
Concepción M, et al. 2021[a]	Metformin 850 mg TID and insulin during hospitalization	None	Bilateral and benign	*RET* proto-oncogene
Sosa-Pagan M, et al. 2020[17]	Metformin 1 g BID, and insulin during hospitalization	None	Left, unilateral and benign	Not specified
Leng O, et al. 2019[18]	36 IU insulin (insulin detemir 24 IU/day, insulin aspart 12 IU TID)	None	Left, unilateral and benign	SDH-A gene
Cha J, et al. 2018[19]	154 IU insulin (insulin glargine 68 IU/day, insulin aspart 28 IU TID)	None	Left, unilateral and benign	SDH-B gene
Mesmar B, et al. 2017[15]	Case 1: Insulin 45 IU/day	Metformin	Left, unilateral and benign	No genetic testing was performed
	Case 2: Insulin 70 IU/day	Metformin + glipizide	Left, unilateral and benign	
Hirai H, et al. 2016[20]	Insulin 40 IU/day	None	Right, unilateral and benign	
Gallagher E, et al. 2011[21]	Insulin 110 IU/day	Glipizide	Right, unilateral and benign	
Murao K, et al. 2007[22]	Insulin 38 IU/day	Insulin 27 IU/day	Right, unilateral and benign	
Rofougaran R, et al. 1997[23]	Insulin 40 IU/day	None	Left, unilateral and benign	
Isotani H, et al. 1996[24]	Insulin 52 IU/day	None	Right, unilateral and benign	

Abbreviations: BID = 2 times a day; TID = 3 times a day; SDH = succinate dehydrogenase.
[a] This study.

Proposed mechanisms include direct stimulation of glucose production, the reduction of insulin secretion, a decrease of peripheral insulin sensitivity, and stimulation of lipolysis in adipose tissue, which offers an alternative substrate for several tissues.[1] The predominant mechanism involves epinephrine rather than norepinephrine.[13] Epinephrine inhibits β-cell insulin secretion via stimulation of α2-adrenergic receptors. In the liver, it activates β2-adrenoceptors to enhance glycogenolysis transiently and gluconeogenesis in a sustained way. This hepatic gluconeogenesis is fueled by precursors such as lactate, alanine, and glycerol and generated by β2-adrenergic stimulation of muscle glycolysis and adipose tissue lipolysis. Lipolysis in adipose tissue is also stimulated via β1- and β3-adrenoceptors. In addition, epinephrine can impair glucose utilization in the muscle through direct β2-adrenergic effects.[11]

Pheochromocytomas are treated, in most cases, by laparoscopic adrenalectomy with prior antihypertensive treatment. Historically, experts have recommended bilateral adrenalectomy even with only single adrenal gland involvement. However, because of the risk of adrenal insufficiency, most experts currently recommend unilateral adrenalectomy in unilateral tumors and adrenal surgery with cortical preservation and close monitoring of remaining tissue in patients with remaining adrenal gland or bilateral pheochromocytoma.[13] Unfortunately, there is no experience with this type of surgical treatment in our country.

The increase in adrenergic secretion can generate overt diabetes mellitus or worsen pre-existing diabetes, with substantial improvement in insulin sensitivity and/or secretory ability following surgical cure of pheochromocytoma.[14–16] There are cases reported in the literature that confirm the benefit of surgery in the improvement or remission of diabetes (Table 2); however, this is the first case reported in which the mutation of the *RET* proto-oncogene was documented as the etiology of bilateral pheochromocytoma. Our patient underwent bilateral adrenalectomy, subsequently achieving diabetes remission 1 year after surgery. These results can also occur after successful treatment of secondary diabetes in other endocrinopathies, such as Cushing's syndrome and acromegaly.[11]

Conclusion

To our knowledge, surgical remission of diabetes in a patient with bilateral pheochromocytoma and *RET* proto-oncogene mutation has not been previously reported. Although diabetes secondary to endocrine disorders is not frequent, timely recognition and treatment of the underlying condition are important to potentially achieve diabetes remission and prevent its long-term complications.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Moghetti P. Diabetes Secondary to Endocrine Disorders and PCOS. In: Bonora E, DeFronzo R, eds. *Diabetes Complications, Comorbidities and Related Disorders*. Springer Nature; 2019:1–19.
2. Karasek D, Shah U, Frysak Z, Stratakis C, Pacak K. An update on the genetics of pheochromocytoma. *J Hum Hypertens*. 2013;27:141–147.
3. Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer*. 2014;14:108–119.
4. Fishbein L, Leshchiner I, Walter V, et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer Cell*. 2017;31:181–193.
5. Farrugia FA, Martikos G, Tzanetis P, et al. Pheochromocytoma, diagnosis and treatment: review of the literature. *Endocr Regul*. 2017;51:168–181.
6. Santos P, Pimenta T, Taveira-Gomes A. Hereditary pheochromocytoma. *Int J Surg Pathol*. 2014;22:393–400.
7. Adas M, Koc B, Adas G, Yalcin O, Celik S, Kemik Ö. Pitfalls in the diagnosis of pheochromocytoma: A case series and review of the literature. *J Epidemiol Res*. 2016;2:49–55.
8. Sanchez A, Candel MF, Albarracín A. Hereditary paraganglioma-pheochromocytoma syndrome. *Med Clin*. 2018;151:e57–e58.
9. Rodriguez JM, Balsalobre M, Ponce JL, et al. Pheochromocytoma in MEN 2A syndrome. Study of 54 patients. *World J Surg*. 2008;32:2520–2526.
10. Crona J, Taïeb D, Pacak K. New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocr Rev*. 2017;38:489–515.
11. Jennings RE, Hanley NA. Endocrine Disorders that Cause Diabetes. In: Holt R, Cockram C, Flyvbjerg A, Goldstein B, eds. *Textbook of Diabetes*. 5th ed. John Wiley & Sons; 2017:272–290.
12. Xu G, Liu B, Sun Y, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ*. 2018;362:k1497.

13. Resmini E, Minuto F, Colao A, Ferone D. Secondary diabetes associated with principal endocrinopathies: the impact of new treatment modalities. *Acta Diabetol*. 2009;46:85–95.
14. Wiesner TD, Blüher M, Windgassen M, Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab*. 2003;88:3632–3636.
15. Mesmar B, Poola-Kella S, Malek R. The physiology behind diabetes mellitus in patients with pheochromocytoma: a review of the literature. *Endocr Pract*. 2017;23:999–1005.
16. Komada H, Hirota Y, So A, et al. Insulin secretion and insulin sensitivity before and after surgical treatment of pheochromocytoma or paraganglioma. *J Clin Endocrinol Metab*. 2017;102:3400–3405.
17. Sosa-Pagan M, Sarmiento-Ramon J, Panunti B. Lifestyle modifications or adrenalectomy? pheochromocytoma presenting with new onset diabetes mellitus. *J Endocr Soc*. 2020;4:A104.
18. Leng O, Madathil A. Remission of longstanding insulin-treated diabetes mellitus following surgical resection of pheochromocytoma. *AACE Clin Case Rep*. 2019;5:e62–e65.
19. Cha J, Khurram M, Gerret L, Epstein P, Baregamian N, Hendrickson C. Case of reversible diabetes mellitus in the setting of benign pheochromocytoma. *J Clin Transl Endocrinol Case Rep*. 2018;10:1–3.
20. Hirai H, Midorikawa S, Suzuki S, Sasano H, Watanabe T, Satoh H. Somatostatin secreting pheochromocytoma mimicking insulin-dependent diabetes mellitus. *Intern Med*. 2016;55:2985–2991.
21. Gallagher EJ, Courgi R, Heiba S, Tamler R. Resolution of insulin-requiring diabetes in a liver transplant recipient after treatment of a pheochromocytoma: case report and review of literature. *Minerva Endocrinol*. 2011;36:341–345.
22. Murao K, Imachi H, Sato M, et al. A case of pheochromocytoma complicated with slowly progressive type 1 diabetes mellitus and chronic thyroiditis. *Endocrine*. 2007;32:350–353.
23. Rofougaran R, Mooraki A, Bastani B. Insulin-requiring diabetes mellitus. hyperlipidemia, and anginal chest pains as prominent features of pheochromocytoma. *Am J Nephrol*. 1997;17:474–476.
24. Isotani H, Fujimura Y, Furukawa K, Morita K. Diabetic ketoacidosis associated with the pheochromocytoma of youth. *Diabetes Res Clin Pract*. 1996;34:57–60.