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CASE REPORT

Case Report: Pheochromocytoma Presenting with Cushing's Syndrome and Hyperglycemia

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Introduction: Pheochromocytomas are catecholamine-producing neuroendocrine tumors that arise from the adrenal medulla. Pheochromocytomas typically present with uncontrollable or paroxysmal hypertension that can be accompanied by other common initial symptoms, including headache, diaphoresis, arrhythmia, and pallor. Given the morbidity and mortality associated with undiagnosed pheochromocytomas, and their potential for treatment, primary care physicians should consider this tumor type, and other endocrinological phenomena, when evaluating new onset hyperglycemia.

Clinical Findings: Patient G was a 76-year-old female who presented in her primary care office with newly uncontrollable hyperglycemia. During initial evaluation, her clinical condition deteriorated rapidly. Her laboratory studies revealed markedly elevated cortisol, adrenocorticotropic hormone (ACTH), and urine metanephrines. Imaging revealed a 3-cm left adrenal mass. Evaluation of ACTH and cortisol levels became complicated by discovery of a lung mass.

Clinical Course: Left adrenalectomy led to resolution of hyperglycemia, catecholamine excess, and Cushing's Syndrome. Tissue pathology of the pheochromocytoma identified ACTH receptor positivity.

Conclusions: Pheochromocytoma is a rare but possible cause of Cushing's Syndrome. Patient G's resolution of hypercortisolemia after successful resection of the pheochromocytoma indicate the tumor's role in her hyperglycemia and Cushing's Syndrome. Despite the well-known association of uncontrollable or paroxysmal hypertension with pheochromocytoma, presenting symptoms vary significantly among patients. The heterogeneity of this neoplasm's presentation highlights the role primary care can play in building this rare diagnosis into the differential early in the disease course.

Keywords: pheochromocytoma, Cushing's Syndrome, hyperglycemia, case report

Patient G was a 76-year-old non-obese female with a medical history of type II diabetes mellitus and breast cancer in remission. In the year before presentation, she had normotensive blood pressure and did not report headaches, sweating, or palpitations. In July 2020, she reported severe hyperglycemia, although her blood pressure remained normotensive in initial visits. A laboratory work-up was initiated (Table 1). The patient also reported insomnia, fatigue, and weight loss. Her primary care physician ordered a computerized tomography (CT) scan of the abdomen and pelvis due to concerns for underlying malignancy based on leukocytosis. The scan showed a left adrenal mass measuring 3.7 x 3.2 cm. Given the CT results, Patient G's physician ordered additional endocrine labs. Patient G had high ACTH levels, prompting evaluation with a CT scan of the chest, which showed a 2.5-cm spiculated mass in the lung. Her severe hyperglycemia continued into August, requiring emergency department visits, despite metformin and sliding-scale insulin therapy. Readings also indicated hypertensive blood pressure. Systolic pressure readings remained under 190 mmHg, and diastolic pressures remained under 100 mmHg. Guidelines by the International Society of Hypertension state that severe hypertension is 200/120 mmHg.[1]

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Table 1. Select Laboratory Testing Performed Between July 2020 and August 2020

Test	Reference range	Result
Hemoglobin A1c	4.5%-5.7%	7.2%
Average blood glucose	70-99 mg/dL	311 mg/dL
Thyroid-stimulating hormone	0.270-4.200 uIU/mL	0.231 uIU/L
Free thyroxine	0.90-1.70 ng/dL	0.88 ng/dL
Cortisol (post-dexamethasone 1 mg overnight)	0.0-5.0 ug/dL	118 ug/dL
Cortisol (morning)	6.0-18.4 ug/d	128 ug/dL
Normetanephrine, plasma free	<0.90 nmol/L	6.2 nmol/L
Metanephrine, plasma free	<0.50 nmol/L	2.5 nmol/L
Adrenocorticotropic hormone (morning)	7.2-63 pg/mL	368 pg/mL
Urine (24 hour)		
Catecholamine, norepinephrine	15-80 mcg	917 mcg
Catecholamine, epinephrine	<21 mcg	248 mcg
Metanephrine	21-153 mcg/g	4095 mcg
Normetanephrine	108-524 mcg/g	3920 mcg
Norepinephrine	7-85 mcg/g	1881 mcg
Epinephrine	2-16 mcg/g	552 mcg
Dopamine	40-390 mcg/g	183 mcg

Table 2. Select Post-Operative Laboratory Testing from October 2020

Test	Reference range	Result
Adrenocorticotropic hormone (morning)	7.2-63 pg/mL	9.3 pg/mL
Cortisol (morning)	6.0-18.4 ug/dL	16.0 ug/dL
Hemoglobin A1c	4.5%-5.7%	6.0%
Normetanephrine, plasma free	<0.90 nmol/L	0.92 nmol/L
Metanephrine, plasma free	<0.50 nmol/L	<0.20 nmol/L

Based on her severe weakness and altered mental status, Patient G was transferred to XYZ Hospital for her increasingly complex condition in mid-August 2020. Her lab tests showed hypokalemia, elevated liver enzymes, and leukocytosis. A metaiodobenzylguanidine scan located the previously identified left adrenal mass.

During her hospital stay, Patient G underwent a left adrenalectomy that extracted a pheochromocytoma of approximately 3 cm. The tumor displayed “patchy positivity” for ACTH and “marked diffuse adrenal cortical hyperplasia, consistent with ectopic ACTH production.” Patient G was discharged to outpatient rehabilitation. Post-operatively, her serum cortisol and ACTH levels normalized. Her glucose control improved with elimination of insulin (Table 2). Her blood pressure stabilized and altered mental status resolved. The lung mass raised concerns for paraneoplastic syndrome versus a post-infectious infiltration. However, biopsy of the lung lesion in December 2020 showed a benign pathology.

DISCUSSION

Pheochromocytomas are neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla. A hallmark of pheochromocytomas is excess catecholamine production. Clinical symptoms of these tumors include sustained, uncontrollable hypertension or paroxysmal hypertension. The hypertension phenotype depends on the amount and pattern of catecholamine secretion from the tumor, which can vary from continuous (causing sustained hypertension) to sporadic (causing episodic hypertension).[2] Catecholamine excess can also lead to headaches, diaphoresis, arrhythmia, and pallor. Pheochromocytomas only account for 3% of ectopic ACTH Cushing's Syndrome.[3] As such, hyperglycemia and other symptoms associated with Cushing's Syndrome are not considered common clinical manifestations of pheochromocytoma.[4,5]

Pheochromocytomas remain an enigmatic diagnosis due to the myriad of presenting symptoms and the paroxysmal nature of the hypertensive spells. Patient G's presentation of sudden uncontrollable hyperglycemia without severe hypertension represents an unusual case presentation of an already rare tumor type. Pheochromocytomas have incidence rates as low as 0.8 per 100 000 person-years.[6] However, these tumors can be lethal if untreated due to catecholamine crises leading to fatal arrhythmias, stroke, and heart failure.[7]

Even with the pathognomonic presentation of episodic hypertensive spells, pheochromocytomas are notorious for their elusive and capricious presentations. Some research notes that these tumors can be asymptomatic for years and masquerade behind nonspecific symptoms, such as nausea, vomiting, and mildly elevated blood glucose.[8]

A review of the literature revealed up to 78 case studies describing ACTH-producing pheochromocytomas.[9,10,11] One of those reports showed 10% ACTH receptor positivity in the pheochromocytoma pathology, which is consistent with our patient's patchy receptor positivity.[11]

Diagnosis of a pheochromocytoma typically relies on quantifying catecholamine excess by measuring the metabolite metanephrines, with an identifiable tumor on imaging. For Patient G, an adrenal tumor was quickly identified by CT imaging, which prompted assessment of metanephrines. However, evaluation of metanephrines, ACTH, and cortisol levels became complicated by the lung mass identified during initial work-up. Considerations included small-cell lung carcinoma and bronchial carcinoid, requiring further work-up with eventual biopsy. Approximately 25% of ectopic ACTH Cushing's Syndrome is associated with bronchial carcinoid tumor types.[3] Bronchial carcinoid tumors resist feedback inhibition, which is tested during the high-dose dexamethasone suppression test. Small bronchial carcinoid tumors may mimic pulmonary vasculature in appearance, indicating that even minor imaging findings should be evaluated.[12] Ectopic ACTH from a lung mass would be a more likely diagnosis in Patient G's age group. US data indicate the annual incidence of lung neuroendocrine masses is approximately 1.49 per 100 000 persons.[13]

Patient G's medical team resected the adrenal mass due to the risks of catecholamine excess. This resection led to a swift remission of her symptoms. Her serum cortisol and ACTH levels normalized within a month post-operatively. Her glucose control improved with elimination of insulin, her blood pressure stabilized, and her altered mental status resolved. Imaging showed the persistence of the lung lesion prompting further evaluation. CT-guided biopsy of the lung lesion was conducted in December 2020 and showed benign pathology.

Pheochromocytoma is an exceedingly rare but possible cause of Cushing's Syndrome. Patient G's resolution of hypercortisolemia, as well as ACTH receptor positivity of pheochromocytoma, indicate the tumor's role in Patient G's presenting hyperglycemia and Cushing's Syndrome. Case presentations such as this one highlight the diversity of this group of neoplasms and point toward the importance of prompt, thorough evaluation and intervention to minimize morbidity and mortality. Additionally, this case displays the heterogeneity of clinical problems that appear in primary care and emphasizes the importance of thorough evaluation by primary care providers. Perhaps one of the most important first steps in evaluating Patient G was considering pheochromocytoma in the original differential diagnosis by her primary care physician. This diagnostic objectivity allowed Patient G's clinical team to recognize and interpret her unusual presentation and promptly begin treatment, leading to a near complete resolution of her symptoms.

Conflict of Interest: None

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