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CLINICAL VIGNETTE

Pheochromocytoma Found Incidentally Following Routine Annual Screening for Lung Cancer in a Former Smoker

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Introduction

Tumors that involve endocrine glands are usually isolated but may be found as a part of combined disorder where neoplasms involve more than one gland. Multiple endocrine neoplasia disorder (MEN) includes different disorders depending on the glands and types of tumors involved.¹ MEN type 1 (MEN1) is defined by presence of tumors of parathyroid glands (90%), pancreatic islet cells (30-70%), and the anterior pituitary (30-40%). Within this disorder, adrenal cortical tumors are also seen in 40% of cases, bronchopulmonary neuroendocrine tumors (NET) (2%), thymic NET (2%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (8%). Pheochromocytomas are rarely reported (less than 1%).² MEN2a is characterized by medullary thyroid carcinoma (MTC, 90%), pheochromocytoma (50%), parathyroid adenoma (20-30%), while MEN2b include MTC (>90%), pheochromocytoma (40-50%), and other abnormalities such as mucosal neuromas, medullated corneal nerve fibers, megacolon and marfanoid habitus (40-50%).³

Case

A 60-year-old female presented to primary care for an annual physical exam. She had no complaints other than menopausal hot flashes and took no medications other than calcium and vitamin D supplements. Her past medical history was significant for unilateral nephrectomy (for donation), hyperlipidemia, colonic polyps, transiently elevated parathyroid hormone (PTH) twenty years prior, and significant past tobacco use, meeting criteria for annual screening for low-dose lung CT scanning. Family history was notable for first-degree relatives with hypertension (n= 3) and non-small cell lung cancer (n=2), as well as kidney cancer, hyperparathyroidism, and pituitary tumors. Her physical exam was only notable for a blood pressure of 154/84 mmHg with a pulse rate = 62 bpm. Following her visit, she provided home BP readings; all of which were all below 140/90 mmHg.

Low dose screening lung CT found centrilobular emphysema, benign-appearing nodules, which were clustered suggesting possible colonization or infection with atypical bacteria, as well as an area of low density in the left hepatic lobe. Further characterization of the hepatic lesion with MRI confirmed the presence of a hepatic hemangioma and a 3.1 cm right adrenal mass suspicious for pheochromocytoma or metastasis. The patient was referred to endocrinology for further workup.

Additional history obtained by endocrinology included episodic palpitations lasting 30-45 seconds, sometimes accompanied with headaches and rarely followed by vomiting. These episodes occurred weekly and had not increased in frequency over the past year. The patient also reported mild polyuria, polydipsia and chronic nausea. Additional family history of primary hyperparathyroidism was noted.

Subsequent lab testing showed an elevated intact PTH with normal ionized calcium and vitamin D. Pituitary MRI showed heterogeneous enhancement in the lateral portion of the gland without discrete mass. Additional labs were notable for abnormal hormone levels as shown in Table 1. Subsequent PET/CT showed intense DOTATATE activity in the right adrenal mass consistent with pheochromocytoma. Following adrenalectomy, tissue analysis confirmed the diagnosis of a benign pheochromocytoma (Pheochromocytoma of the Adrenal gland Scaled Score=0). Given the presence of mild primary hyperparathyroidism, a single kidney, and decreased renal function, partial parathyroidectomy was performed. Intra-operatively PTH dropped from 82 pg/mL to 38 pg/mL. A follow-up DOTATATE scan was negative and pancreatic laboratory studies remained within normal limits.

Table 1 - Abnormal hormone levels in a patient with an adrenal mass and history of elevated prolactin

Hormone	Observed	Upper limit of normal
Norepinephrine	2255 pg/mL	520 pg/mL
Dopamine	36 pg/mL	20 pg/mL
Metanephrine, free	0.63 nmol	0.49 nmol/L
Normetanephrine, free	10.77 nmol	0.89 nmol/L
Intact PTH	136* pg/mL	51 pg/mL
Prolactin (with dilution)	27.6 ng/mL	23.1 ng/mL
Chromogranin A	360 ng/mL	95 ng/mL
Serum calcium	10.4 mg/dL	10.3mg/dL
Ionized Ca++,Corrected	1.24 mmol/L	1.29 mmol/L
Vitamin D,25-Hydroxy	24 ng/mL	50 ng/mL

* ionized calcium and vitamin D levels were within normal limits

Based on history of mildly elevated prolactin and primary hyperparathyroidism MEN1 was suspected however, genetic

testing was negative for mutations, clinically significant variants, variants of uncertain significance or large gene deletions or duplications in the following 12 genes: FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127 and VHL. Following these negative tests, the patient refused additional genetic testing including BRCA1/2 which was advised due to significant family history of ovarian and breast cancer.

Discussion

This patient's hyperparathyroidism was milder than expected in classical MEN1-associated hyperparathyroidism where most patients will have significant hypercalcemia before age 50.⁴ She presented with pheochromocytoma which is rare with MEN1.² Diagnosis of MEN1 can be made clinically if a patient has two or more primary MEN1-associated endocrine tumors.⁵ Despite the atypical presentation, she met criteria for clinical diagnosis of MEN disorder.

If initial genetic tests are negative, guidelines recommend additional tests. Up to 25% of patients with clinical diagnosis will not have a known mutation.⁶ Clear guidelines for radiologic screening are not established and vary by patient-specific factors and clinical judgement.⁷ Recommendations for screening, monitoring and surveillance are very similar to those for genetically confirmed cases of MEN, including continued surveillance for other MEN-associated tumors and identification of first degree relatives for clinical and biochemical testing.

Our understanding of combined endocrinopathies continues to evolve with the growing body of case reports and database of genes implicated in these disorders.⁸

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