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. Intraoperatively 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]

REFERENCES

1. **Grajo JR, Paspulati RM, Sahani DV, Kambadakone A**. Multiple Endocrine Neoplasia Syndromes: A Comprehensive Imaging Review. *Radiol Clin North Am*. 2016 May;54(3):441-51. doi: 10.1016/j.rcl.2015.12.001. Epub 2016 Mar 10. Review. PubMed PMID: 27153782.
2. **Okada R, Shimura T, Tsukida S, Ando J, Kofunato Y, Momma T, Yashima R, Koyama Y, Suzuki S, Takenoshita S**. Concomitant existence of pheochromocytoma in a patient with multiple endocrine neoplasia type 1. *Surg Case Rep*. 2016 Dec;2(1):84. doi: 10.1186/s40792-016-0214-x. Epub 2016 Aug 30. PubMed PMID: 27572829; PubMed Central PMCID: PMC5005233.
3. **King KS, Pacak K**. Familial pheochromocytomas and paragangliomas. *Mol Cell Endocrinol*. 2014 Apr 5;386(1-2):92-100. doi: 10.1016/j.mce.2013.07.032. Epub 2013 Aug 7. Review. PubMed PMID: 23933153; PubMed Central PMCID: PMC3917973.
4. **Giusti F, Marini F, Brandi ML**. Multiple Endocrine Neoplasia Type 1. 2005 Aug 31 [updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from http://www.ncbi.nlm.nih.gov/books/NBK1538/PubMed PMID: 20301710.
5. **Turner JJ, Christie PT, Pearce SH, Turnpenny PD, Thakker RV**. Diagnostic challenges due to phenocopies: lessons from Multiple Endocrine Neoplasia type1 (MEN1). *Hum Mutat*. 2010 Jan;31(1):E1089-101. doi: 10.1002/humu.21170. PubMed PMID: 19953642.
6. **Cavaco BM, Domingues R, Bacelar MC, Cardoso H, Barros L, Gomes L, Ruas MM, Agapito A, Garrão A, Pannett AA, Silva JL, Sobrinho LG, Thakker RV, Leite V**. Mutational analysis of Portuguese families with multiple endocrine neoplasia type 1 reveals large germline deletions. *Clin Endocrinol (Oxf)*. 2002 Apr;56(4):465-73. PubMed PMID: 11966739.
7. **Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML; Endocrine Society**. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012 Sep;97(9):2990-3011. doi: 10.1210/jc.2012-1230. Epub 2012 Jun 20. Review. PubMed PMID: 22723327.
8. **Buzzola R, Kurukulasuriya LR, Touza M, Litofsky NS, Brietzke S, Sowers JR**. A Possible New Multiple Endocrine Neoplasia Mutation in a Patient with a Prototypic Multiple Endocrine Neoplasia Presentation. *Cardiorenal Med*. 2016 Feb;6(2):129-34. doi: 10.1159/000440985. Epub 2016 Jan 15. PubMed PMID: 26989398; PubMed Central PMCID: PMC4789941.

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