Incidental Detection of Synchronous Medullary Thyroid Carcinoma with Bilateral Adrenal Pheochromocytoma on Iodine-123 Metaiodobenzylguanidine Scintigraphy, Leading to Diagnosis of Multiple Endocrine Neoplasia 2A

Asif Ali Fakhri, Paul David Rodrigue, Mustafa Aladin1, Aun Hussain

Departments of Nuclear Medicine and Molecular Imaging and 1Internal Medicine, University at Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York, USA

Abstract

We report a case of a 29-year-old female with the family history of medullary thyroid carcinoma (MTC) presenting with hematuria and tachycardia, who was found to have bilateral adrenal masses on abdominal computed tomography and biochemical testing compatible with pheochromocytoma. Iodine-123 (I-123) metaiodobenzylguanidine (MIBG) scintigraphy for preoperative planning prior to planned adrenalectomy revealed incidental synchronous unifocal MTC, along with expected bilateral adrenal pheochromocytomas. Pathology confirmed these findings, and subsequent genetic testing confirmed a rearranged during transfection proto-oncogene mutation on exon 11, confirming the clinical diagnosis of multiple endocrine neoplasia 2A (MEN 2A). The unexpected incidental finding of synchronous MTC highlights the importance of considering MEN in the differential diagnosis when encountered with newly diagnosed pheochromocytoma and highlights the utility of I-123 MIBG scintigraphy in diagnostic workup of newly diagnosed pheochromocytoma.

Keywords: Iodine-123 metaiodobenzylguanidine, medullary thyroid carcinoma, multiple endocrine neoplasia, pheochromocytoma, rearranged during transfection

Introduction

Multiple endocrine neoplasia (MEN) is an autosomal dominant genetic disorder in which the patient is predisposed to the development of tumors involving multiple endocrine organs. MEN subtype 2A (MEN 2A) is a rare subtype that is typically characterized by predisposition to developing specifically medullary thyroid carcinoma (MTC), pheochromocytoma, and primary parathyroid hyperplasia. Although there can be variable timeframe of manifestation, MTC is usually diagnosed first.1 The genetic defect in MEN 2A involves the rearranged during transfection (RET) proto-oncogene on chromosome ten. As expected from its autosomal dominant inheritance pattern, men and women with Type 2A are affected in equal proportions.2
Iodine-123 (I-123) metaiodobenzylguanidine (MIBG) scintigraphy is a proven reliable noninvasive technique for prompt confirmation of catecholamine releasing tumors.\cite{2} Like the prior gold standard radiopharmaceutical agent I-131 MIBG, I-123 MIBG is highly sensitive and specific for pheochromocytoma, with reported sensitivity of 83–100% and specificity of 95–100%.\cite{2} It serves as a confirmatory imaging test in patients with biochemical and anatomic imaging evidence pheochromocytomas, and thus helps in presurgical planning. Previously, radiolabeled MIBG scintigraphy has been shown to also be useful for the detection of MTC. The sensitivity is much less at 20–64%; however, the specificity remains high at >95%.\cite{2-5}

**Case Report**

A 29-year-old female initially presented with progressive hematuria and tachycardia. A contrast-enhanced computed tomography (CT) of the abdomen and pelvis which revealed bilateral adrenal masses. Biochemical testing was done which revealed markedly elevated plasma metanephrines at four times the upper limits of normal, plasma normetanephrine at six times the upper limits of normal, and plasma total metanephrines at five times the upper limits of normal.

Given the biochemical and CT findings, a diagnosis of pheochromocytoma was made. She was referred for I-123 MIBG scintigraphy for confirmation. The patient was injected with 333 MBq of I-123 MIBG whole body planar and single-photon emission CT (SPECT) imaging was acquired using a dual-headed SPECT camera 24 h following injection. She received thyroid blockade using 1% lugol solution for 2 days prior and 2 days subsequent to the I-123 MIBG injection.

The scan revealed unequivocal I-123 MIBG avid lesions within both adrenal glands and an additional focal I-123 MIBG avid lesion in the left thyroid lobe [Figures 1 and 2].

The patient subsequently underwent successful bilateral robotic adrenalectomy. Surgical pathology was consistent with bilateral adrenal pheochromocytoma. A needle biopsy of the left thyroid lobe lesion revealed MTC.

The patient had a reported family history of a maternal great-aunt with MTC. In the setting of family history, the patient’s diagnosis of MTC and bilateral adrenal pheochromocytoma, a clinical diagnosis of MEN 2A was made. She underwent genetic testing for RET oncogene mutation, which revealed a mutation in exon 11 of the RET gene. This finding is seen in 98% of families with MEN 2A.\cite{1}

**Discussion**

MEN 2 is relatively rare with estimated occurrence of 1 out of 200,000 live births. Among these, MEN 2A makes up approximately 70–80% of the cases.\cite{1} Patients with MEN 2A most commonly manifest clinically with MTC, and it usually present at a younger age, often prior to age 35.\cite{1} Pheochromocytoma is usually present after MTC or synchronously, and up to 60% of patients with MEN 2 may not develop pheochromocytoma at all.\cite{6,7} Nonetheless, differential diagnosis of MEN 2, and therefore, synchronous MTC, should remain in consideration.

Radiolabeled MIBG is useful because it targets both of these tumors, since both MTC and pheochromocytomas are of neural crest cell origin. Incidental synchronous detection of pheochromocytoma and MTC was first reported by Endo \textit{et al.} in 1984 using the established I-131 scintigraphy.\cite{3} Subsequent studies looked at the efficacy of MIBG radiolabeled scintigraphy in detecting MTC.\cite{8} However, we highlight a novel case in which there is incidental synchronous detection of previously undiagnosed MTC during confirmatory workup for pheochromocytoma specifically utilizing MIBG radiolabeled to I-123.
Since its Food and Drug Administration approval in 2008, use of I-123 MIBG has expanded due to practical reasons including: Lower radiation dose to the patient superior imaging quality, namely the ability to perform SPECT which provides much improved lesion contrast [Figure 2].\(^2\) Given the annual incidence of pheochromocytoma is approximately 2–8 million persons/year, this case represents the potential simultaneous benefit of I-123 MIBG scintigraphy as both a rapid confirmatory tool to confirm the diagnosis of adrenal pheochromocytoma, in a patient with strong biochemical and anatomic imaging evidence, and a rapid screening tool for MEN 2, specifically for the presence of synchronous MTC.\(^3\) Ultimately, histopathology and genetic testing would obviously be required, but a prompt and more definitive diagnosis on the basis of I-123 MIBG scintigraphy could guide earlier treatment planning.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
The authors declare no conflicts of interest.

**References**

1. Moline J, Eng C. Multiple endocrine neoplasia type 2: An overview. Genet Med 2011;13:755-64.
2. Ilias I, Divgi C, Pacak K. Current role of metaiodobenzylguanidine in the diagnosis of pheochromocytoma and medullary thyroid cancer. Semin Nucl Med 2011;41:364-8.
3. Endo K, Shiomi K, Kasagi K, Konishi J, Torizuka K, Nakao K, et al. Imaging of medullary thyroid cancer with 131I-MIBG. Lancet 1984;2:233.
4. Rufini V, Castaldi P, Treglia G, Perotti G, Gross MD, Al-Nahhas A, et al. Nuclear medicine procedures in the diagnosis and therapy of medullary thyroid carcinoma. Biomed Pharmacother 2008;62:139-46.
5. Yin H, Wu H, Zhang Y, Tian W, Jiang X, Zhou X, et al. Diagnosis of multiple endocrine neoplasia type 2A in patients with positive thyroid imaging by iodine-131 metaiodobenzylguanidine scintigraphy. Clin Nucl Med 2011;36:772-5.
6. Fishbein L. Pheochromocytoma and paraganglioma: Genetics, diagnosis, and treatment. Hematol Oncol Clin North Am 2016;30:135-50.
7. Tsang VH, Tacon LJ, Learoyd DL, Robinson BG. Pheochromocytomas in multiple endocrine neoplasia type 2. Recent Results Cancer Res 2015;204:157-78.
8. Baulieu JL, Guilloteau D, Delisle MJ, Perdrisot R, Gardet P, Delépine N, et al. Radiolabeled meta-iodobenzylguanidine uptake in medullary thyroid cancer. A French cooperative study. Cancer 1987;60:2189-94.
9. Stamm M, Abele JT. Streamlining the imaging of clinically suspected pheochromocytoma: Using urine metanephrines to decrease imaging costs. Can Assoc Radiol J 2014;65:372-8.