

Published in final edited form as:

Endocr Relat Cancer. 2012 February ; 19(1): 83–93. doi:10.1530/ERC-11-0243.

False-Negative ¹²³I-MIBG SPECT Is Most Commonly Found in SDHB-Related Pheochromocytoma or Paraganglioma with High Frequency to Develop Metastatic Disease

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Abstract

Objective—The purpose of this study was to present the characteristics and outcome of patients with proven pheochromocytoma or paraganglioma who had false-negative ¹²³I-MIBG SPECT.

Methods—Twenty one patients with false-negative ¹²³I-MIBG SPECT, (6 males, 15 females) aged 13–55 years (mean 40.9 years) were included. We classified them according to the stage of the disease as non-metastatic or metastatic at the time of false-negative ¹²³I-MIBG SPECT study, the location and size of the tumor, plasma and urinary catecholamine and metanephrine levels, genetic mutations, and outcome in terms of occurrence and progression of metastases and death.

Results—Thirteen patients were evaluated for metastatic tumors while 8 others were seen for non-metastatic disease. All primary tumors and multiple metastatic foci did not show avid ¹²³I-MIBG uptake regardless of the tumor diameter. The majority of patients had extra-adrenal tumors with hypersecretion of normetanephrine or norepinephrine. *SDHB* mutation was present in 52% (n=11) of cases, *RET* mutation in 4% (n=1), and the rest were apparently sporadic. Twenty four percent (n=5) had metastatic disease on initial presentation. Fourteen patients were followed-up

DECLARATIONS OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

All authors were involved in conceptualizing this research paper and contributed in the writing and editing of the final manuscript. Furthermore, Jay S. Fonte, M.D. and Jeremyjones F. Robles M.D. were involved in data gathering. Jay S. Fonte, M.D., Karel Pacak, M.D., Ph.D., D.Sc., Clara C. Chen, M.D., James Reynolds, M.D., and Millie Whatley reviewed the nuclear imaging studies of the patients. Jay S. Fonte M.D., Karel Pacak, M.D., Ph.D., D.Sc., and Alexander Ling, M.D. reviewed the CT scan and MRI of the patients. Karel Pacak, M.D., Ph.D., D.Sc., Tito Fojo, M.D., Karen Adams, Jay S. Fonte, M.D. and Jeremyjones F. Robles M.D. were involved in the management of the patients included in the study. Jay S. Fonte, M.D. and Karel Pacak, M.D., Ph.D., D.Sc. wrote the initial manuscript.

for 3–7 years. From them, 71% (n=10) had metastatic disease and majority had *SDHB* mutation. Nine are still alive while 5 (4 were *SDHB*) died due to metastatic disease.

Conclusion—A false-negative ^{123}I -MIBG SPECT is frequently related to metastatic tumors and usually due to *SDHB* mutations with unfavourable prognosis. We, therefore, recommend that patients with false-negative ^{123}I -MIBG SPECT be tested for *SDHB* mutations and to undergo more regular and close follow-up.

Keywords

^{123}I -MIBG; pheochromocytoma; paraganglioma; succinate dehydrogenase subunit B; catecholamines; metanephrines

INTRODUCTION

Pheochromocytoma (PHEO) and paragangliomas (PGL) are tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglionic tissues, respectively (DeLellis *et al.* 2004). These tumors express cellular membrane norepinephrine transporter (NET) through which catecholamines can enter and deposited inside neurosecretory granules via the vesicular monoamine transporter systems (VMATs). Metaiodobenzylguanidine (MIBG) is a guanethidine analogue resembling norepinephrine (NE) that can enter chromaffin cells through active uptake via NET or passive diffusion and is stored in catecholamine containing neurosecretory granules (Vaidyanathan 2008, Havekes *et al.* 2008, Bomanji *et al.* 1987, Sisson *et al.* 1981). This characteristic make MIBG very useful and extremely specific for the diagnostic localization of PHEO and PGL when labelled with radiotracers such as iodine-123 (^{123}I) or iodine-131 (^{131}I) (Jacobson *et al.* 2010, Meyer-Rochow *et al.* 2010, Havekes *et al.* 2008, Ilias and Pacak 2004, Timmers *et al.* 2009, Sisson *et al.* 1981, Goldsmith 2009). In addition, ^{131}I -MIBG is also used for the treatment of metastatic PHEO and PGL that demonstrate avid MIBG uptake (Loh *et al.* 1997, Gonias *et al.* 2009, Rose *et al.* 2003, Castellani *et al.* 2010).

It was previously shown that $^{123/131}\text{I}$ -MIBG scintigraphy is comparable with other nuclear imaging studies such as 2- ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F -FDG PET), ^{18}F -fluorodopamine (^{18}F -FDA) and ^{18}F -fluorodopa (^{18}F -DOPA) in the detection of primary, sporadic, and non-metastatic PHEO and PGL (Timmers *et al.* 2009). However, the sensitivity of $^{123/131}\text{I}$ -MIBG scintigraphy in the detection of metastatic tumors and familial PHEO and PGL is somewhat suboptimal compared with other nuclear imaging studies (van der Harst *et al.* 2001, Taïeb *et al.* 2004, Ilias *et al.* 2003, Fottner *et al.* 2010, Kauhanen *et al.* 2009, Fiebrich *et al.* 2009, Goldsmith 2009, Shulkin *et al.* 1999). It is also less sensitive in the detection of extra-adrenal and small PHEO and PGL (van der Harst *et al.* 2001, Bhatia *et al.* 2008, Wiseman *et al.* 2009). Since the uptake of MIBG was shown to be well correlated with the presence of NET or VMATs; the number of neurosecretory granules and perhaps the degree of differentiation of tumor cells controlling the expression of NET may play an important role in a successful application of $^{123/131}\text{I}$ -MIBG scintigraphy (Bomanji *et al.* 1987, Eisenhofer *et al.* 2001, Fottner *et al.* 2010). Nevertheless, $^{123/131}\text{I}$ -MIBG scintigraphy remains widely used because it is readily available and less expensive than ^{18}F -FDA and ^{18}F -FDOPA PET.

Initially we observed that patients with PHEO and PGL, especially those growing rapidly, presented with negative ^{123}I -MIBG single photon emission computed tomography (SPECT). Then some of them with rapidly progressing PHEO and PGL were found to be associated with succinate dehydrogenase subunit B (*SDHB*) gene mutation. Therefore, we hypothesized that negative ^{123}I -MIBG SPECT, regardless whether in patients having a primary or recurrent tumor or metastatic disease, would point towards the presence of

SDHB mutation. Proving this hypothesis would alert physicians to initiate *SDHB* mutation testing, especially in those patients with a negative family history of this disease. Furthermore, we hypothesized that these ^{123}I -MIBG SPECT negative tumors could reflect more aggressive behavior (as also commonly seen in *SDHB* patients) and should also alert physicians to perform more regular follow-up including biochemical as well as imaging tests.

MATERIALS AND METHODS

Patients

Official results of ^{123}I -MIBG SPECT of patients seen at the National Institutes of Health (NIH) from 2002 through March 2011 for evaluation of PHEO and PGL were reviewed. Patients with false-negative ^{123}I -MIBG SPECT at any point from initial presentation to follow-up were identified and included in the present study if they were diagnosed with PHEO and PGL based on the clinical presentation, specific biochemical tests including measurement of catecholamine and metanephrines in either plasma or urine, PHEO and PGL specific imaging studies, and histopathological confirmation of resected tumors. All patients were part of an Institutional Review Board approved prospective study of patients with known or suspected PHEO and/or PGL at NIH. All patients provided informed consent.

Biochemical Tests

Patients were asked to abstain from acetaminophen for 5 days, caffeinated and decaffeinated products, smoking, and alcohol for 24 hours prior to blood extraction and 24-hour urine collection. For plasma catecholamine and metanephrine determination, a cannula was inserted in the forearm for intravenous access. Patients were in the supine position without a pillow in a quiet room for 20–30 minutes before and during collection. As soon as blood was collected, it was placed on ice and stored in -80°C until testing. Basal plasma levels of catecholamines and metanephrines were measured by high performance liquid chromatography (HPLC). For urinary catecholamine and metanephrine determination, total volume collected over 24 hours was used and measured by HPLC or liquid chromatography-tandem mass spectrometry.

Imaging Tests

Computed Tomography (CT)—Axial images of the neck, chest, abdomen, and pelvis were obtained after administration of oral and intravenous low-osmolar contrast. Multiple helical axial images at 2.5 mm and 5 mm thick were obtained in the neck and from the thoracic inlet to the symphysis pubis, respectively.

Magnetic Resonance Imaging (MRI)—Axial images of the head, neck, chest, abdomen and pelvis were obtained. Axial T1, axial STIR, and post-contrast fat-saturated axial T1-weighted images were obtained through the neck while T1- and T2-weighted scans and STIR images were obtained in the chest. Scans were obtained before, during, and after intravenous injection of 14 mL Magnevist. In the abdomen, multiple sequences including axial T2-weighted (one without fat suppression with respiratory trigger; another one with fat suppression and suspended respiration) and 2D in and out of phase T1 weighted images prior to, and multiphase 3D volume images in axial planes, single venous coronal following vascular contrast administration (18cc Magnevist) obtained at 3T. If clinically indicated, MRI of the spine was obtained with sagittal T1-weighted and sagittal STIR images of the cervical, thoracic, and lumbar spine without administration of contrast material. Axial T2-weighted images were acquired at selected levels.

¹²³I-MIBG SPECT—Patients were required to withdraw medications that can potentially interfere with MIBG uptake (e.g. labetalol, monoamine oxidase inhibitors, phenylpropanolamine, tricyclic and other antidepressants, or reserpine) at least 1 week before the procedure. To protect the thyroid from accumulation of free radioactive iodine, patients received 100 mg of saturated solution of potassium iodide by mouth twice a day for 4 days starting the night before ¹²³I-MIBG administration. Whole body planar and single photon emission computed tomography imaging were done mostly 24 hours and some 48 hours after intravenous administration of 8.4–11 mci (mean 10.18) ¹²³I-MIBG. Attenuation CT scan was available in 3 patients.

Other Functional Imaging Studies—¹⁸F-FDG PET/CT, ¹⁸F-FDA PET/CT, ¹⁸F-FDOPA PET were performed. The patients were asked to fast for at least 6 hrs prior to intravenous injection of ¹⁸F-FDA (1 mci), ¹⁸F-FDG (15.9 mci), and ¹⁸F-FDOPA (12 mci). Patients were also asked to refrain from caffeine, tobacco and alcohol for at least 12 hrs. Capillary blood glucose was measured before ¹⁸F-FDG PET/CT. A low-dose, noncontrast, nondiagnostic CT was obtained for attenuation correction and anatomic localization. For ¹⁸F-FDOPA PET, patients received 2 mg/kg carbidopa orally as pretreatment 1 hr before radiotracer injection.

Genetic Testing

Genetic testing was performed at the Department of Human Genetics of the Pittsburgh University Medical Center Clinic, Pennsylvania and at the Mayo Clinic Laboratories, Minnesota, USA. A *stepwise* approach to genetic testing was performed based on the most likely gene mutation to be present based on the clinical presentation, biochemical phenotype, and the location of tumor(s). Patients were tested for von Hippel-Lindau, multiple endocrine neoplasia type 2 (MEN 2), SDHB, succinate dehydrogenase subunit C, and D gene mutations (Maher and Eng 2002). Not all currently known susceptibility genes for PHEO and PGL were tested in our patients if a specific gene mutation causing the disease was already found. Furthermore, gene testing for TMEM127, SDHA, SDHAF2, and MAX gene mutations was not performed (Hensen and Bayley 2011, Comino-Méndez *et al.* 2011).

Data Analysis—¹²³I-MIBG studies were reviewed separately by 2 experienced nuclear medicine physicians (C.C. and J.R.) who were blinded to any anatomic imaging studies and clinical history of patients. Physiologic uptake in the adrenal gland was carefully distinguished from abnormal uptake using the widely accepted four-point visual scale: (0) no increased activity demonstrated in one or both adrenal glands; (1) faint increased activity demonstrated in one or both adrenal glands; (2) moderate increased activity in one or both adrenal glands less than or equal to that of the liver; (3) intense increased activity in one or both adrenal glands greater than the liver. Scores of 0 to 2 were classified negative or physiologic uptake while score of 3 was classified positive for PHEO or PGL.

All patients with adrenal tumor had histopathological confirmation of PHEO. Thus, a false-negative ¹²³I-MIBG scan among these patients was defined as the absence of, or radiotracer uptake in the adrenal gland less than that of the liver (score 0–2). On the other hand, patients with multiple metastatic lesions or inoperable tumors may not have pathologic confirmation of metastatic PHEO or PGL. Therefore, a false-negative ¹²³I-MIBG scan in this group was defined as the absence of radiotracer uptake in a tumor of a patient who had clinical, biochemical, and anatomical and specific nuclear imaging studies clearly consistent with PHEO and PGL.

Metastatic PHEO or PGL was defined as the presence of tumor at sites where chromaffin tissues are not normally located such as bones, liver, lungs, and lymph nodes. Multifocal disease was defined as presence of multiple tumor foci, presenting synchronously or metachronously (new primary) to the original tumor, whereas recurrence was defined as reappearance of the disease as documented at reintervention or by combined biochemical and radiological tests after previous complete eradication of the tumor.

RESULTS

Patient Characteristics

We included 21 patients (6 males, 15 females) aged 13–55 years (mean 40.9 years), 7 of whom were referred for evaluation and management of possible PHEO and PGL while 14 other patients were referred after previous surgery of their primary tumor (adrenal PHEO, n=4; urinary bladder PGL, n=3; retroperitoneal and extra-adrenal PGL, n=6; carotid body tumor, n=1) (Table 1). After a thorough evaluation, 8 patients were found to have non-metastatic tumor and 13 others have metastatic disease.

Plasma metanephrines were elevated in 17 patients (81%) [5 had both normetanephrine (NMN) and metanephrine (MN) elevated, 12 had elevated NMN only] while 4 others had normal levels. Plasma catecholamines were elevated in 15 patients (71%) [1 had elevated NE, epinephrine (EPI), and dopamine (DA), 1 had elevated NE and EPI, 5 had elevated NE and DA, 6 had elevated NE only, 1 had elevated EPI only, and 1 had elevated DA only]. Urinary metanephrines and catecholamines were available in 13 patients only. Eleven patients (85%) had elevated urinary metanephrines (2 had elevated total metanephrines, NMN and MN; 9 had elevated total metanephrines and NMN). Ten patients (83%) had elevated urinary catecholamines (1 had elevated NE and EPI, 2 had elevated NE and DA, 7 had elevated NE only).

Results of anatomical and functional imaging studies are presented in Table 2. All patients had tumors (primary or metastatic) that failed to accumulate ^{123}I -MIBG at first presentation to NIH except patients no. 11, 15, 18, and 19 in whom false-negative scans were observed on follow-up (second ^{123}I -MIBG SPECT) when they developed a metastatic disease (patient no. 18) or progression of a known metastatic disease (patients no. 11, 15, and 19). Of the 8 patients with non-metastatic tumor (patients no. 1–8), anatomical and nuclear imaging studies other than ^{123}I -MIBG SPECT/CT showed adrenal gland PHEO (n=6; 5 unilateral, 1 bilateral), paraesophageal PGL (n=1), and paraaortic PGL (n=1) which were confirmed by histopathology after surgery. In patient no. 2 with MEN 2 syndrome, ^{18}F -FDG PET/CT further showed increased uptake of radiotracer in the skull, neck, and mediastinum which were proven to be related to medullary tumor of the thyroid after excision. None of them was found to have multifocal and metastatic disease as proven by multiple imaging studies together with normalization of plasma metanephrines and catecholamines postoperatively.

Among 13 patients with metastatic disease, metastases were noted in the lungs (n=8), multiple bony sites (n=9), lymph nodes (n=12), liver (n=5), and other soft tissues (n=3). Despite multiple tumor sites found per patient, none showed avid ^{123}I -MIBG uptake. Patient no. 10 with metastatic disease was concomitantly found to have another primary tumor in the right adrenal gland while patient no. 9 developed another primary tumor in bilateral carotid bodies with metastatic disease to the liver, lungs, lymph nodes and bones as shown in Figure 1 after removal of a urinary bladder PGL. In these patients, both primary and metastatic tumors had no uptake of ^{123}I -MIBG.

Of the 7 patients with adrenal PHEO (5 primary and non-metastatic; 1 recurrence; 1 new primary with metastases), the mean largest diameter of the tumor was 4.3 cm (range: 1.5 to 7

cm). In 1 patient with primary tumor on the right carotid body and in another patient with left paraaortic PGL, the tumor measured 0.8 cm and 1.5 cm, respectively.

Eleven (52%) patients were found to have *SDHB* mutation and 1 (4%) was found to have MEN 2 syndrome while the rest of the patients presented with apparently sporadic PHEO and/or PGL. Among *SDHB*-related tumors, 9 were associated with metastatic disease, 1 had multifocal tumor, and 1 had non-metastatic tumor.

Outcome Analysis

Patients with false-negative ^{123}I -MIBG SPECT not later than 2008 were included for outcome analysis (n=19). Five patients were excluded due to lack of follow-up (n=4) and infection with human immunodeficiency virus (n=1). A total of 14 cases were analyzed with a mean follow-up period of 5 years (range: 2 – 7) after the first documented false-negative ^{123}I -MIBG SPECT at NIH (Table 3). On initial presentation at NIH, 4 (29%) of these patients had no metastasis, while 10 (71%) had metastatic disease.

Of the 4 patients with non-metastatic PHEO or PGL, none developed metastatic disease until March 2011 while 1 patient (patient no. 7) developed another primary tumor in the left carotid body and paraesophageal PGL after about 6 years following a false-negative ^{123}I MIBG SPECT. Two of the non-metastatic cases were due to *SDHB* mutation while the other 2 were apparently sporadic. All patients are still alive.

Of the 10 patients with metastatic disease, 9 (90%) had *SDHB* mutation while the other 1 had apparently sporadic PHEO or PGL. Patient no.12 had multiple metastases to the lungs and left paraaortic lymph nodes which were excised. Patient no.15 had multiple metastases to the bones, liver and lymph nodes and was given chemotherapy with cyclophosphamide + vincristine + dacarbazine (CVD), sunitinib, bortezomib, 17-DMAG, and external beam radiotherapy. Patient no.16 who had multiple metastases to the bones, lungs, liver and lymph nodes received chemotherapy with CVD and underwent radiofrequency ablation of liver metastases. Patients no. 11 and 17 who had metastases to the bones, liver, lungs and lymph nodes were treated with CVD and 17-DMAG, respectively. Patient no. 18 had gamma knife radiotherapy of a carotid body tumor invading the skull which was later on resected. She also received CVD chemotherapy. Patient no. 19 eventually had metastatic lesions with avid uptake on subsequent ^{123}I -MIBG SPECT and therefore underwent ^{131}I -MIBG treatment but due to persistent disease, she also received temozolamide. Patient no. 21 had resection of the periaortic lymph node and hilar metastases and developed another primary tumor in the left adrenal gland 6 years after the initial diagnosis which was resected as well. Five (55%) (4 *SDHB* + 1 sporadic) died due to overwhelming metastases after a mean of 10.4 years (range: 3–17 years) and 5.2 years (range: 3–7 years) after the initial diagnosis of PHEO or PGL and development of metastatic disease, respectively. Sixty percent of deaths occurred within 5 years after the diagnosis of metastatic disease. Four other patients (2 *SDHB* + 2 sporadic) had progressive disease within a mean follow-up of 7.25 years (range: 6–9 years) while one other patient had stable metastatic disease.

DISCUSSION

The present study presents detailed characteristics and outcomes of patients with false-negative ^{123}I -MIBG SPECT. Majority had primary tumors of extra-adrenal chromaffin tissues, noradrenergic biochemical phenotype, metastases, and over half had mutation in *SDHB*. The latter comprise 25% and 69% of patients with non-metastatic and metastatic PHEO or PGL, respectively. To our best knowledge, this is the first paper to show that a false-negative ^{123}I -MIBG SPECT in patients with PHEO or PGL follow a more aggressive course and are frequently linked to the presence of *SDHB* mutation. In general, it is

estimated that the rate of malignancy among patients with PHEO and PGL is about 10%–30% and that about 10% have metastatic disease upon initial presentation (Ilias *et al.* 2004, Goldstein *et al.* 1999). It is also estimated that about one third or more of PHEOs and PGLs have a defined genetic cause (Amar *et al.* 2005, Erlic *et al.* 2005, Mannelli *et al.* 2009). Nevertheless, in the present study, we have shown that among patients with false-negative ^{123}I -MIBG SPECT, the rate of malignancy was higher at 62% (13 out of 21) and 24% (5 out of 21) had metastatic disease on initial presentation. Furthermore, 57% (12 out of 21) were due to a genetic mutation, with 92% (11 out of 12) of these cases being linked to *SDHB* mutation.

It is well established that PHEO or PGL due to *SDHB* mutation is associated with shorter survival (Amar *et al.* 2007) and higher incidence of malignancy (Timmers *et al.* 2009, Brouwers *et al.* 2006, Burnichon *et al.* 2009). It is estimated that the malignancy rate of *SDHB*-related PHEO or PGL is at least 30% and often much higher and the 5-yr probability of survival after the diagnosis of first metastasis among these patients drop to 36% in contrast to 67% among patients without that mutation (Amar *et al.* 2007). In our study, *SDHB* mutation accounted for 69% of metastatic disease and 80% of mortality.

In the present study, 44% (4 out of 9) of patients with apparently sporadic PHEO and PGL were found to have metastatic disease resulting in death in 1 patient within 6 years after the diagnosis of metastasis. In contrast to these data, it was previously shown that the rate of malignancy among apparently sporadic tumor is only 9% (Bravo and Tagle 2003). It should be further emphasized that of the 5 patients who had metastatic disease upon initial diagnosis, 3 had apparently sporadic tumor. These suggest that negative ^{123}I -MIBG SPECT points toward unfavourable outcome which may be independent of *SDHB* mutation.

There are several factors that can cause a false-negative ^{123}I -MIBG study. Medications such as labetalol, reserpine, calcium channel blockers, and antidepressants may interfere with MIBG uptake (Solanski *et al.* 1992; Havekes *et al.* 2008). $^{123}/^{131}\text{I}$ -MIBG scintigraphy has been shown to have lower sensitivity for small tumors (van der Harst *et al.* 2001, Bhatia *et al.* 2008, Wiseman *et al.* 2009). However, 2 of our patients had adrenal PHEOs measuring 7 cm with false-negative scan by ^{123}I -MIBG SPECT. Although the sensitivity of $^{131}/^{123}\text{I}$ -MIBG scintigraphy is also generally suboptimal for extra-adrenal PGLs, we have also included in this series a patient with mediastinal PGL measuring 8 cm that had false-negative ^{123}I -MIBG SPECT. The suboptimal sensitivity of $^{123}/^{131}\text{I}$ -MIBG for metastatic PHEO and PGL has also been shown in previous studies and is related to the dedifferentiation that results in loss of NETs among these tumors (Timmers *et al.* 2009, Ilias *et al.* 2003). The limited sensitivity of $^{123}/^{131}\text{I}$ -MIBG scintigraphy for familial cases of PHEO and PGL has also been documented (van der Harst *et al.* 2001, Bhatia *et al.* 2008, Taïeb *et al.* 2004, Ilias *et al.* 2003, Fottner *et al.* 2010, Timmers *et al.* 2009). Thus, ^{123}I -MIBG scintigraphy is not recommended for these patients and negativity may reflect aggressive behaviour. Studies have also shown that a predominant NE and NMN secretion predicts negative ^{123}I -MIBG scintigraphy which was also observed in the current study (van der Harst *et al.* 2001, Fottner *et al.* 2010). However, one study has shown that the uptake of MIBG was not correlated with the plasma or urinary catecholamine levels but with the amount of neurosecretory granules within the tumor (Bomanji *et al.* 1987). Recently, it was shown that the lack of VMAT-1 expression explains false-negativity for MIBG scintigraphy (Fottner *et al.* 2010).

The present study has some limitations. Most patients that were referred to NIH due to metastatic disease did not have preoperative $^{123}/^{131}\text{I}$ -MIBG scintigraphy. Furthermore, the data may be affected by referral bias and follow-up period for some patients seen at NIH for their primary tumors was relatively short to certainly conclude a non-metastatic disease. It is

also recommended that a head to head comparison be made as to the outcomes of SDHB-related tumors with avid and false-negative ^{123}I -MIBG SPECT.

In conclusion, we have shown that a false-negative ^{123}I -MIBG SPECT is frequently related to metastatic tumors, usually due to *SDHB* mutations with unfavourable prognosis. We, therefore, recommend that patients with false-negative ^{123}I -MIBG SPECT be tested for *SDHB* mutations and should undergo more regular and close follow-up.

Acknowledgments

FUNDING

This work was supported by the Intramural Research Program of the National Institutes of Child Health and Human Development/National Institutes of Health.

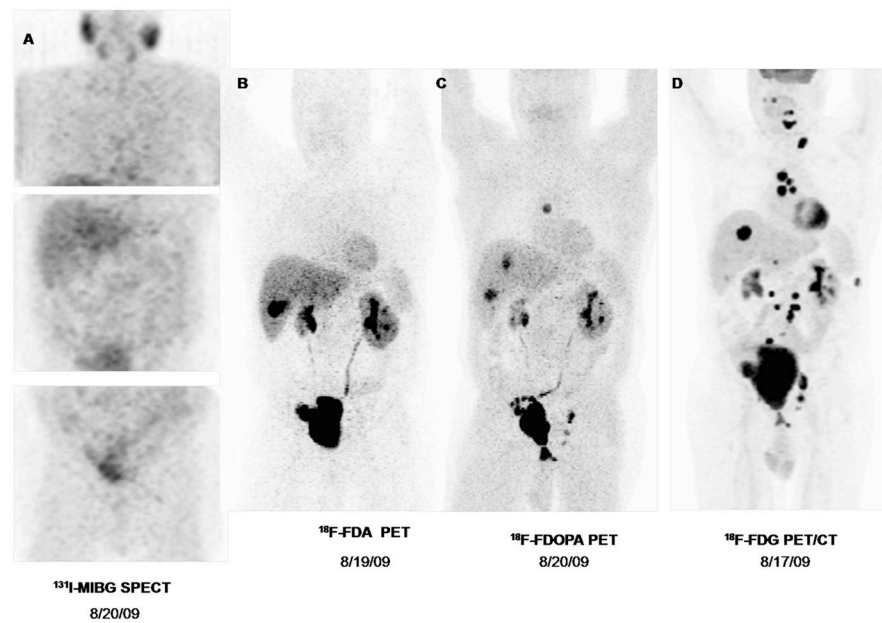
Jay S. Fonte, M.D. and Jeremy Jones F. Robles M.D. acknowledge the staff of the Section of Endocrinology and Metabolism, Department of Medicine, University of Santo Tomas Hospital, Manila, Philippines and the Thomasian Endocrine Progress Inc. for their invaluable support during their training at the National Institutes of Health.

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**FIGURE 1.**

Nuclear imaging studies of a 55-year old male with metastatic pheochromocytoma who tested negative for succinate dehydrogenase B, C, and D mutation. Primary tumor was found in the urinary bladder and was removed with en bloc cystectomy, prostatectomy, with lymphatic node dissection and creation of ileal neobladder in 2005. In 2009, he was diagnosed with metastatic disease with false-negative iodine-123 metaiodobenzylguanidine single photon emission computed tomography (^{123}I -MIBG SPECT/CT). At NIH, ^{123}I -MIBG SPECT/CT (A) was also negative but other nuclear imaging such as ^{18}F -fluorodopamine (^{18}F -FDA) (B), ^{18}F -dihydroxyphenylalanine (^{18}F -FDOPA) (C), and especially 2- ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F -FDG PET) (D) showed multiple metastatic foci in lymph nodes, lungs, and liver. He underwent radiofrequency ablation of liver lesions. A repeat ^{18}F -FDG PET/CT after 3 months showed evidence of progression.

TABLE 1

Characteristics of Patients at the Time of False Negative ¹²³I-MIBG SPECT

Patient	Age (yr)/Sex	Reason for consult at NIH	Hypersecretion in Plasma		Hypersecretion in Urine		Gene Mutation
			Meta-nephrines	Cate-cholamines	Meta-nephrines	Cate-cholamines	
1	13/F	P	NMN, MN	NE, E, DA	--	--	Apparently sporadic
2	47/F	P	NMN, MN	E	NMN, MN, T	None	<i>RET</i>
3	51/F	P	NMN, MN	NE, E	NMN, MN, T	NE, E	Apparently sporadic
4	61/M	P	None	DA	--	--	<i>SDHB</i>
5	49/F	P	NMN	NE	NMN, T	NE	Apparently sporadic
6	46/F	P	NMN, MN	None	--	--	Apparently sporadic
7	36/F	New P	NMN	NE	NMN, T	NE	<i>SDHB</i>
8	40/F	R	NMN	NE	NMN, T	NE, DA	Apparently sporadic
9	55/M	Met + New P	NMN	NE, DA	NMN, T	NE	Neg for <i>SDHx</i>
10	48/F	Met + New P	NMN	NE, DA	NMN, T	NE, DA	<i>SDHB</i>
11	42/F	Met + New P	NMN	NE, DA	NMN, T	NE	<i>SDHB</i>
12	36/F	Met	NMN	NE	NMN, T	NE	<i>SDHB</i>
13	32/M	Met	NMN, MN	None	None	None	Apparently sporadic
14	47/F	Met	None	None	--	--	<i>SDHB</i>
15	43/F	Met	NMN	NMN	NMN, T	None	<i>SDHB</i>
16	34/M	Met	NMN	NE, DA	--	--	<i>SDHB</i>
17	37/M	Met	NMN	NE, DA	--	--	<i>SDHB</i>
18	43/F	Met	None	None	--	--	<i>SDHB</i>
19	45/F	Met	NMN	NE	None	NE	Apparently sporadic
20	33/M	Met	None	None	--	--	<i>SDHB</i>
21	22/F	Met	NMN	NE	NMN, T	NE	Apparently sporadic

Adr: adrenal gland; DA: dopamine; E: epinephrine; F: female; M: male; MN: metanephrine; Met: metastasis; NE: norepinephrine; Neg: Negative; NMN: normetanephrine; P: primary tumor; R: recurrence; *RET*: rearranged during transfection; *SDHB*: succinate dehydrogenase subunit B; *SDHD*: succinate dehydrogenase subunit D; T: total metanephrines; *VHL*: von Hippel-Lindau

--: not available

TABLE 2
Comparative Imaging Studies of Patients with False-Negative ¹²³I-MIBG SPECT

Patient	CT	MRI	¹²³ I-MIBG	^{18F} -FDA	^{18F} -FDOPA	^{18F} -FDG-PET
1	R adr	NA	Neg	NA	NA	R adr
2	R+L adr	R+L adr	Neg	Neg	NA	R parietal skull*, R upper posterior neck*, R mediastinum*
3	L adr	L adr	Neg	L adr	NA	L adr
4	L paraaortic L renal mass**	L paraaortic	Neg	Neg	Neg	L paraaortic, and L kidney
5	R adr	R adr	Neg	R adr	NA	NA#
6	R+L adr	R+L adr	Neg	Neg	R adr	NA
7	Para-esophageal	Para-esophageal	Normal adr uptake	Neg	NA	Paraesophageal
8	R adr	NA	Neg	Neg	NA	Neg
9	Liver, lung, LN, B, bilateral carotid	Liver, LN, B, bilateral carotid	Neg	B	B, Liver, LN	R carotid, soft tissues adjacent to C2 and C3 cervical vertebrae, B, liver, LN
10	B, LN, lungs, R adr	NA	Normal adr uptake	LN	NA	NA
11	B, lungs, Liver periaortic	R adr B, liver, retro-peritoneal L periaortic	Normal adr uptake	Liver, bone, LN, soft tissues in the abdomen	NA	B, L upper abdomen in the region of the pancreas and toward the L side of the upper abdomen, liver, LN and soft tissues in the abdomen
12	Lung, pelvic LN	Lung, pelvic LN	Normal adr uptake	Neg	NA	Lungs, pelvic LN ^{^NA}
13	B	B	Normal adr uptake	B	NA	B
14	Lung, LN, B	B [^]	Normal adr uptake	Neg	Neg	B, Lungs
15	B, liver, LN, Infraplenic	B, liver, LN	Normal adr uptake	B, infraplenic	NA	R posterior medial lung, B, L lateral abdomen, liver
16	B, lungs, LN, liver, L paraaortic mass, intrathoracic prevertebral mass	B, liver, LN, L paraaortic mass, intrathoracic prevertebral mass [^]	Normal adr uptake	Neg	NA	Lungs, LN, B, liver lower abdomen extending to the midline
17	LN, lungs, B, liver	B, LN, liver	Normal adr uptake	LN	Neg	LN, B, liver
18	LN	LN	Normal adr uptake	Neg	NA	B, LN
19	Lungs, LN	Lungs, LN	Normal adr uptake	R mediastinum at the hilar area, L lung, LN	NA	Lungs, LN
20	R carotid LN in the chest	R carotid LN in the chest	Neg	Neg	R carotid	LN in the chest
21	LN	LN	Normal adr uptake	LN	LN	LN

Adr: adrenal gland, B: bones, L: left, LN: lymph nodes, Neg: Negative; R: right; ^{18}F -FDA; ^{18}F -fluorodopamine, ^{18}F -FDOPA; ^{18}F -dihydroxyphenylalanine, ^{18}F -FDG PET; 2- ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography

* Medullary Thyroid Cancer-related

** Left renal mass: renal cell carcinoma by histopathology

available from outside prior to referral to NIH with increased uptake in the right adrenal gland

[^] MRI of the chest not done

^{^^^} outside scan not available for review

TABLE 3Outcome of Patients with False-Negative ^{123}I -MIBG SPECT

	Living	Dead
N	9	5
Tumor Type		
<i>Nonmetastatic</i>	4	0
<i>Metastatic</i>	5	5
Primary Tumor Location		
<i>Adrenal</i>	2	2
<i>Extra-adrenal</i>	7	3
Gene Mutation		
<i>SDHB</i>	5	4
<i>Sporadic</i>	4	1