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Misdiagnosis of Paraganglioma by ^{123}I-mIBG Without Stable Iodine Blockade of Thyroidal Radioiodine Uptake

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Iodine-123/iodine-131 (^{123}I/^{131}I)-metaiodobenzylguanidine (mIBG) scan is an established tool for the localization and treatment of neuroendocrine tumors such as paragangliomas (PGL). To minimize thyroid irradiation by the radioactive iodine in the mIBG preparation, blockade of thyroidal iodine uptake with high doses of stable iodine used to be given routinely as part of all mIBG protocols. As ^{123}I is now more frequently utilized than ^{131}I, concern about thyroid radiation has lessened and thyroid blockade is often considered unnecessary. However, in certain situations, the lack of thyroid blockade can significantly impact treatment decisions. This report describes 2 patients who had mediastinal masses incidentally discovered on CT scans, and on further evaluation were found to have symptoms suggesting catecholamine excess with mildly elevated plasma normetanephrine levels. ^{123}I-mIBG scans were performed without thyroid blockade, which demonstrated accumulation of tracer in the masses that were therefore deemed positive for PGL. Both patients underwent surgical resection of the masses with their surgical pathology revealing ectopic thyroid tissue (ETT). These cases illustrate that if appropriate thyroid blockade is not performed, ETT concentrating radioiodine from mIBG can lead to falsely positive mIBG scans and unnecessary surgical procedures. We conclude that in the setting of a mass suspicious for PGL in a location potentially representing ETT, such as the mediastinum, thyroid blockade should be employed for mIBG protocols to avoid false positive scans caused by ETT.

Key Words: ^{131}I/^{123}I-metaiodobenzylguanidine, ectopic thyroid tissue, paraganglioma metanephrine, normetanephrine

The iodine-123/iodine-131 (^{131}I/^{123}I)-metaiodobenzylguanidine (mIBG) scan is generally used to localize neuroendocrine tumors, especially those of neuroectodermal origin, such as pheochromocytomas and paragangliomas (PPGL) [1]. mIBG scan is an important diagnostic tool for the initial workup, staging, and follow-up of these tumors and their metastases. However, this imaging technique has limitations. The reported sensitivities

Abbreviations: CT, computed tomography;ETT, ectopic thyroid tissue;mIBG, metaiodobenzylguanidine;NIS, sodium-iodide symporter;PET, positron emission tomography; PGL, paraganglioma;PPGL, pheochromocytomas and paragangliomas;SPECT, single-photon emission computed tomography;SSKI, supersaturated solution potassium iodine;TPO, thyroid peroxidase;TSH, thyrotropin (thyroid-stimulating hormone).

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and specificities for the diagnosis of PPGL have ranged widely, from 56% to 88% and 70% to 100%, respectively [2, 3]. Factors that may limit the specificity of the scan in the diagnosis of neuroendocrine tumors include non–catecholamine-secreting tumors such as carcinoids and medullary thyroid carcinoma, as well as confounding of images from organs that demonstrate physiologic uptake of the tracer, such as the thyroid gland, lungs, liver, gastrointestinal tract, urinary bladder, and adrenals, as well as by the sympathetic innervation of these organs [3, 4]. In addition, multiple medications, such as alpha blockers, calcium channel blockers, sympathomimetics, neuroleptics, antihistamines, opioids, and tricyclic antidepressants, can impair the scan's diagnostic sensitivity [1, 3].

Another concern with mIBG scans is the radiation exposure, particularly when the beta particle emitter ^{131}I is used as the tracer. To avoid thyroidal side effects related to ^{131}I exposure, it has largely been replaced for diagnostic imaging by the pure gamma emitter ^{123}I [5], which provides 100-fold lower estimated tissue radiation dose per millicurie compared with ^{131}I [6]. Previously, when ^{131}I was widely used for diagnostic scans, blockade of radioiodine uptake by the thyroid gland was considered an important part of the mIBG protocol. With more widespread use of ^{123}I, there has been less concern about potential thyroid radiation and in many centers, pretreatment with stable iodine is less frequently used in mIBG imaging protocols. Here we present 2 patients with mediastinal masses that illustrate the potential impact of not providing saturated iodine pretreatment prior to ^{123}I-mIBG on clinical decision-making and patient outcomes.

Case 1

A 49-year-old woman was admitted to the psychiatry unit with new onset mania. She endorsed insomnia, nights sweats, and significant cognitive decline over the prior 5 months. During her 1-month hospitalization, treatment with olanzapine and divalproex sodium did not relieve her symptoms. Therefore, the inpatient psychiatry team pursued an extensive evaluation that revealed elevated levels of plasma metanephrine, 87 pg/mL (normal range ≤57 pg/mL), and normetanephrine, 485 pg/mL (normal range ≤148 pg/mL). The patient had no history of hypertension. She did have a constant sense of overwhelming anxiety, but denied paroxysmal symptoms suggesting catecholamine excess, including headaches, diaphoresis, palpitations, or panic attacks. In addition, there was no family history of diagnosis with or symptoms of PPGL or related syndromes (MEN 2, neurofibromatosis, or Von Hippel Lindau syndrome). On physical exam, the patient was normotensive (BP 121/69 mmHg), mildly tachycardic (HR 104 bpm), and anxious-appearing with pressured speech.

Furthermore, the psychiatry team pursued extensive imaging searching for occult tumors that may have caused a paraneoplastic syndrome to explain her psychosis. A CT scan of her abdomen and pelvis with IV contrast showed normal-appearing adrenal glands. A CT scan of the chest with IV contrast identified a 1.2 × 1.0 × 0.6 cm enhancing nodule posterior to the manubrium in the anterior mediastinum, inferior to the thyroid gland, which measured 175 Hounsfield units (HU) in the venous phase (Fig. 1A). The radiology report suggested the differential diagnosis for this nodule to include ectopic thyroid tissue (ETT), a parathyroid nodule, or a paraganglioma (PGL). An ^{123}I-mIBG SPECT-CT done without stable iodine pretreatment revealed focal uptake in a retromanubrial soft tissue nodule, which was deemed consistent with a PGL; the eutopic thyroid gland was also seen (Fig. 1B, C). At this point, the endocrinology team was consulted, and recommended repeating laboratory testing after olanzapine was discontinued. Her repeat testing off olanzapine showed normal 24-hour urinary metanephrine and normetanephrine levels, and a mildly elevated plasma normetanephrine of 197 pg/mL with normal plasma metanephrine. Urinary fractionated catecholamines including epinephrine, norepinephrine, and dopamine were all normal. Other laboratory values obtained showed calcium, parathyroid hormone, free T4 (thyroxine), and thyrotropin (thyroid-stimulating hormone) within the reference range.

Despite the low level of suspicion for PGL, the patient elected to undergo resection of the mediastinal mass to establish a definitive diagnosis. The patient was started on alpha

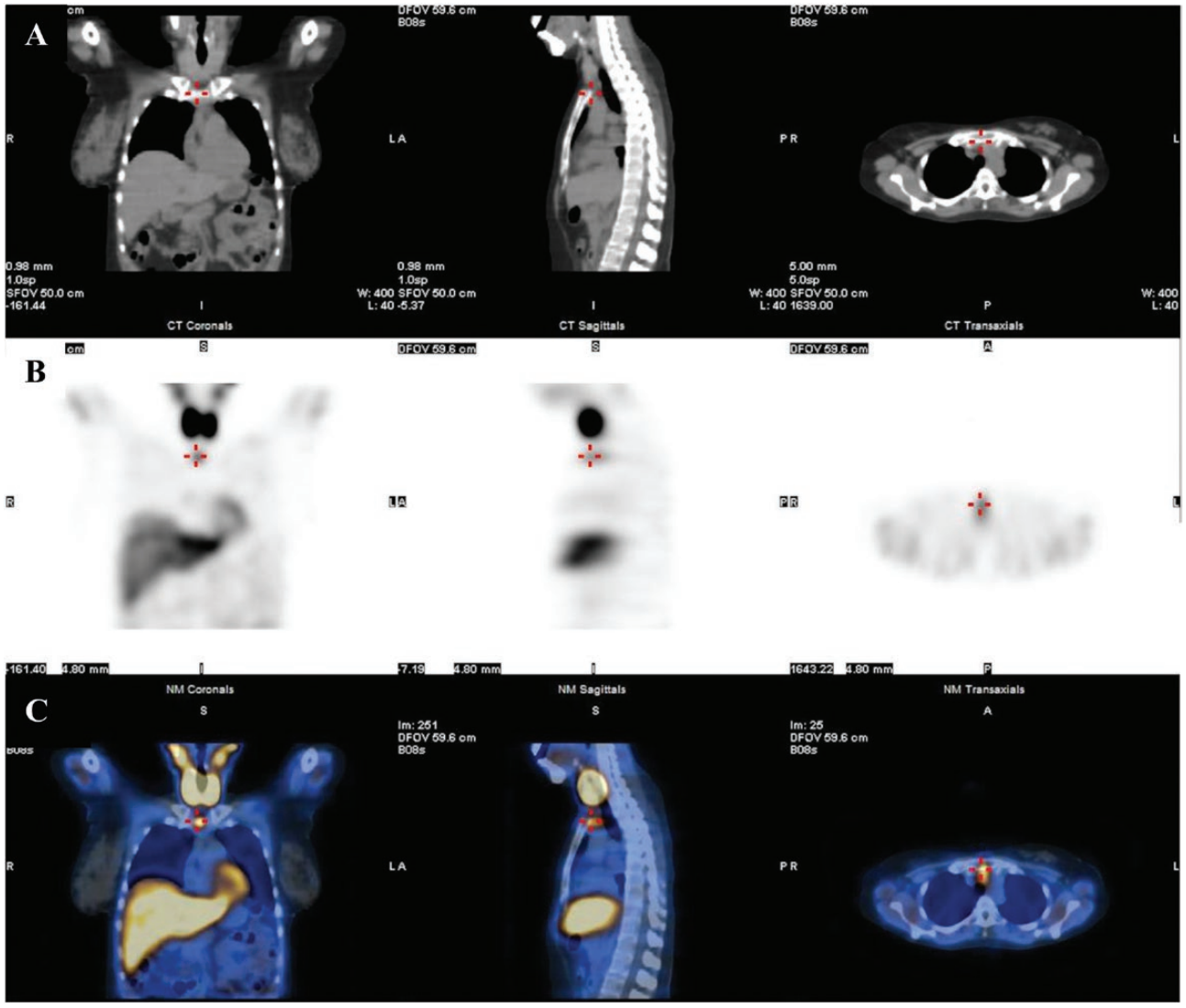

Figure 1. Case 1 ^{123}I-mIBG scan. **A:** CT for localization and attenuation correction. **B:** SPECT images. **C:** Fused SPECT/CT images localizing the lesion to the upper mediastinum.

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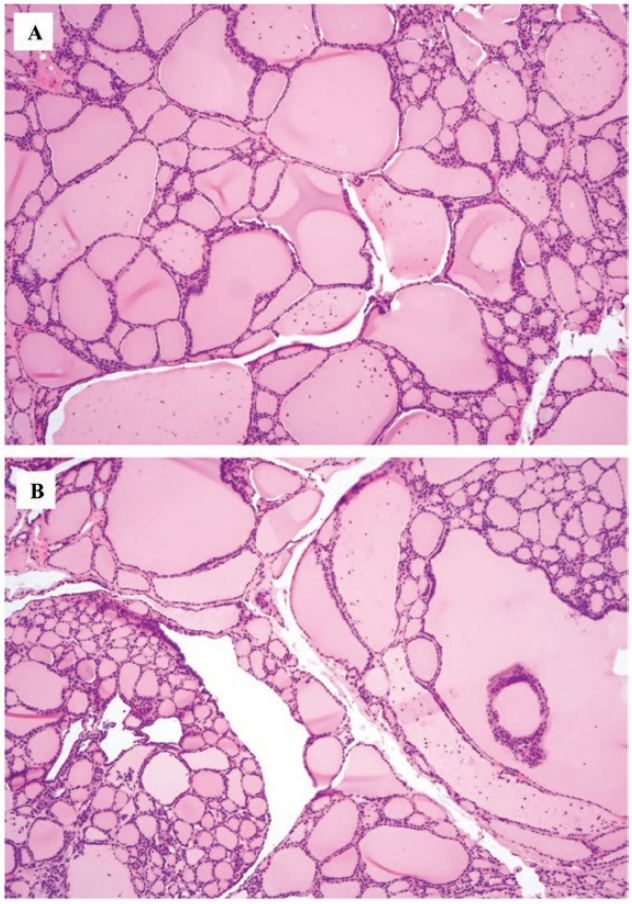

Figure 2. Ectopic thyroid tissue histopathology. A: Case 1, benign thyroid tissue (100×). **B:** Case 2, multinodular hyperplasia (100×).

blockade with doxazosin 1 mg twice daily for 10 days preoperatively and underwent uncomplicated mediastinoscopy for excision of the anterior mediastinal mass. Surgical pathology showed the mass to be benign ETT (Fig. 2A). The patient's psychiatric symptoms persisted for several weeks after excision of the mass, but she ultimately recovered with initiation of an alternate antipsychotic regimen and was discharged home. Repeated 24-hour urine metanephrine and normetanephrine measurements 2 weeks after surgery were within the reference range.

Case 2

A 42-year-old woman with past medical history of cyclic vomiting syndrome and hypertension controlled with amlodipine 10 mg daily, was admitted to the hospital with intractable vomiting. During hospitalization, she was persistently tachycardic, and CT angiography of the chest was obtained to exclude a pulmonary embolism (PE). This was negative for pulmonary embolism but it showed a 2.0 × 1.4 × 2.0 cm nodule inferior to the left thyroid lobe (Fig. 3A). The radiology report suggested the differential diagnosis for this nodule to include a parathyroid adenoma or a PGL. Plasma normetanephrine was mildly elevated, 264 pg/mL (normal range ≤ 148 pg/mL), and plasma metanephrine was undetectable. A 24-hour urine normetanephrine was also mildly elevated, 896 mcg/24 hours (normal range, 88-649 mcg/24 hours), with normal urinary metanephrine, 131 mcg/24 hours. On initial endocrinology assessment, the patient had no history of episodic hypertensive crises, diaphoresis, anxiety, tremors, headaches, palpitations, or chest pain. She had no family history of PPGL or any

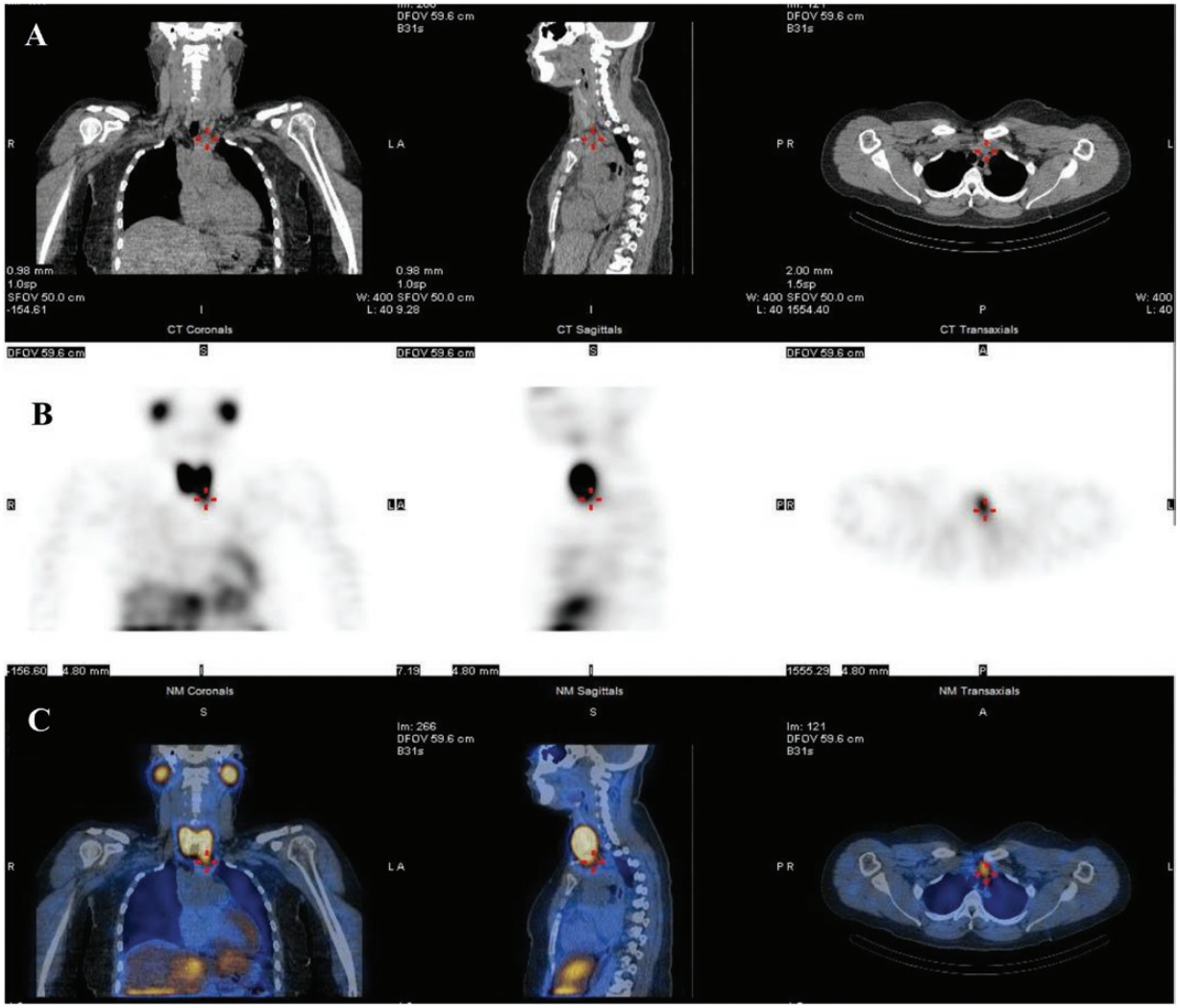

Figure 3. Case 2 ^{123}I-mIBG scan. **A:** CT for localization and attenuation correction. **B:** SPECT images. **C:** Fused SPECT/CT images localizing the lesion to the lower pole of the left thyroid lobe.

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of the associated syndromes. On laboratory evaluation, her calcium, parathyroid hormone, TSH, and free T4 were within the reference range. Plasma fractionated catecholamines including epinephrine, norepinephrine, and dopamine were normal.

A ^{123}I-mIBG planar and single-photon emission computed tomography (SPECT)/CT was obtained without stable iodine pretreatment and showed moderate uptake in the left upper mediastinum at the location of the previously described nodule, measuring 2.0 cm, and considered compatible with a PGL (Fig. 3B and 3C); eutopic thyroid gland was also seen.

Similar to case 1, the patient elected to undergo surgery to establish a definitive diagnosis without any additional testing. She was started on alpha blockade with doxazosin 1 mg daily for about 4 months preoperatively and underwent uncomplicated mediastinoscopic resection of the mediastinal nodule. Her surgical pathology described a 3.0 × 2.8 × 2.3 cm mass consistent with thyroid tissue with multinodular hyperplasia (Fig. 2B). The patient was discharged and recovered without complications. Unfortunately, was subsequently lost to follow-up.

Discussion

Here we report 2 patients whose nonspecific symptoms prompted a broad medical evaluation that revealed mildly elevated normetanephrine levels, and CT scans revealing a mediastinal mass with concerns for a PGL. Subsequent ^{123}I-mIBG scans without stable iodine pretreatment showed focal tracer uptake in these masses, which were interpreted as consistent with PGL. However, on resection of the masses, they proved to be ectopic thyroid tissue (ETT) in both cases.

These 2 cases illustrate the importance of following the proper diagnostic steps in the work-up of patients with suspected catecholamine excess, as not doing so can lead to false positive results and the wrong clinical decisions. First, it is fundamental to obtain a detailed history that includes comorbidities, use of potentially interfering medications, and information about the pattern, duration, and characteristics of the symptoms and/or spells. Neither of these 2 patients had a convincing history of PGL, as evidenced by the lack of family history and typical symptoms. In case 1, her initial biochemical testing results were likely confounded by her anxiety and the use of olanzapine, producing false positive results. In case 2, anxiety and stress related to the patient's hospitalization could explain her abnormal results. In both cases, the degree of normetanephrine elevation was less than 2 to 3 times the upper limit of normal, which argues against PGL as the cause of the patients' symptoms. Second, imaging should only be obtained after unequivocal biochemical confirmation of catecholamine excess, as these imaging techniques are also susceptible to false positive and false negative results. In particular, there was a recent change in our institution's mIBG protocol, where pretreatment with thyroid blockade was eliminated. As seen in these 2 cases, once imaging findings are made available to patients, anxiety regarding the nature of these incidentally found nodules understandably intensifies and may lead to unnecessary surgical procedures. While our discussion will focus on the importance of thyroid blockade for mIBG testing, it should be noted that alternative testing might have been pursued to help clarify the diagnosis in these 2 cases. For instance, in the setting of equivocal biochemical results, a clonidine suppression test can be performed to help with the diagnosis of PPGL [7, 8]. Additionally, it is important to keep in mind that DOTATATE positron emission tomography (PET)/CT has a better sensitivity compared to ^{123}I-mIBG becoming a more favored imaging modality for localizing PPGL [9]. Also, DOTATATE PET/CT or ^{123}I-thyroid scan could have also helped to differentiate between ETT and PGL.

Ectopic thyroid in the mediastinum can be the result of aberrant embryologic migration of the thyroid tissue from the foramen cecum in the primitive foregut toward its eutopic pretracheal position. In addition to the mediastinum, reported positions of ETT resulting from abnormally long descent include the heart, pericardium, esophagus, lung, diaphragm, duodenum, small intestinal mesentery, and adrenal gland [10, 11]. Although most such ETT is in or near the midline, case 2 had tissue that was not located in the midline, emphasizing

that ETT should still be considered even if a mass is not centrally located. These embryologically ectopic sites may represent all of the individual's thyroid tissue, or they may exist along with a eutopic thyroid gland, as was the case in both of these patients. Mediastinal thyroid tissue can also occur in a sequestered substernal goiter, in which a hyperplastic nodule extending from the inferior aspect of the eutopic gland may be tenuously connected or even entirely separated from the body of the thyroid [12]. On CT imaging, ETT is typically well circumscribed, hyperdense, and homogenous with increased attenuation of 60 to 80 HU and avidly enhancing in post-contrast images [13]. The identification of ETT is, of course, usually accomplished by imaging with radioiodine, which in these 2 cases could have allowed detection of ETT prior to surgery.

mIBG was developed in the early 1960s-1970s as a selective adrenergic nerve blocking agent to evaluate adrenal gland physiology. Eventually, scientists combined the benzyl portion of bretylium with the guanidine group of guanethidine to synthesize benzylguanidine-derived compounds [14]. Free radioiodine in the administered agent, which is released when mIBG is metabolized, is concentrated by normal thyroid tissue. To a much lesser extent, mIBG can also be taken up by the sympathetic nerves that innervate the thyroid gland [6].

Blockade of undesirable thyroid gland irradiation can be accomplished by administering a preceding high oral dose of stable iodine—typically supersaturated solution potassium iodine (SSKI) or potassium iodide-iodine (Lugol's solution), depending on the protocol, from 1 hour to 1 to 2 days before the test. When given acutely (eg, hours before the radioiodine), the large amount of stable iodine floods the system, greatly diminishing the uptake of radioiodine by competing with the radioiodine for active transport via the sodium-iodide symporter (NIS) that concentrates iodine in thyrocytes. When stable iodine is given more than 1 day prior to the test it will also inhibit the NIS synthesis, as well as oxidation and organification of iodide catalyzed by thyroid peroxidase, the Wolff-Chaikoff effect [6, 15]. A study evaluating the effects of acute iodine administration on NIS and thyroid peroxidase (TPO) showed that NIS mRNA expression decreased from 6 to 24 hours after iodine exposure, whereas reduction in TPO mRNA and NIS protein expression occurred only after 24 hours, supporting that the Wolff-Chaikoff effect is part of the protective mechanisms when iodine is given at least a day prior to mIBG [16]. There has been controversy whether such thyroid blockade is actually necessary, particularly with the advent of mIBG labeled with ^{123}I rather than ^{131}I imaging.

The European Association of Nuclear Medicine recommended thyroid blockade for ^{123}I-mIBG as part of their guidelines published in 2010 [1]. Since then, no updated guidelines have been issued. In 2014, one study reported that thyroid uptake and scans for patients who were undergoing ^{123}I-mIBG for cardiac imaging were not statistically different between individuals who received stable iodine blockade 1 hour prior to the tracer injection and those who did not receive blockade [6]. The authors suggested that the accumulation of mIBG tracer in the thyroid sympathetic nerves, rather than actual thyroid uptake, resulted in the "uptake" seen in the blocked thyroid [6, 17]. Another study in 2016 [17], conducted in patients undergoing ^{123}I-mIBG for cardiac and neurological conditions (congestive heart failure and Parkinson disease, respectively), reported similar results, suggesting that thyroid blockade may not be justified. The authors concluded that the risks for thyroid complications associated with large amounts of potassium iodide, such as leukopenia and the potential risk for iodine allergy, warrant a revision of imaging guidelines for ^{123}I-mIBG scans. Furthermore, others have argued that the short half-life of ^{123}I-mIBG radioisotope (13.2 hours) and the exceeding low amount of free radioiodine in the preparation (<3%) should mitigate concerns for side effects [6]. Friedman et al [6] pointed out that in older patients there may be less concern for the long-term risk of thyroid neoplasia from the minimal amount of radiation exposure from ^{123}I-mIBG. These studies have led to a decrease in the use of routine thyroid blockade prior to ^{123}I-mBIG, as seen in our institution with the 2 reported cases here.

While the avoidance of thyroid blockade based on thyroid gland safety may be reasonable, this led to the misdiagnosis of mediastinal masses as paragangliomas when they were

actually ETT. A biochemical diagnosis of PPGL should always be first established prior to any diagnostic imaging, but this unfortunately cannot be done with certainty in every case. As seen in the 2 patients reported here, thyroid blockade with high doses of iodine that will eliminate thyroid tissue uptake can be vital in eliminating ETT as a false positive finding for PGL in mediastinal masses. In ETT, the tracer accumulation is primarily due to free iodine absorption, therefore thyroid blockade could be of significant diagnostic assistance. As ETT foci are usually small, it would be very unlikely to find significant sympathetic innervation that could accumulate mIBG. Alternative ways to differentiate between PGL and ETT include thyroid scanning using radioactive iodine.

Currently, our institution has reinstated iodine pretreatment for thyroid blockade for ^{123}I-mIBG scanning after these 2 cases. We provide 0.3 mL (6 drops) of SSKI (300 mg of iodine) 1 hour prior to the tracer injection. Other protocols exist at different institutions, such as starting iodine 1 day before mIBG administration and continuing it for 1 to 2 days for ^{123}I or 2 to 3 days for ^{131}I-mIBG [1]. In addition, prompt communication between endocrinologists and nuclear medicine specialists is important in clinical decision-making regarding timing and necessity of thyroid blockade.

In conclusion, the cases presented here illustrate potential consequences of not blocking the thyroid prior to ^{123}I-mIBG administration. This is particularly critical in the presence of cervical or mediastinal masses, to avoid an incidental finding of ETT. Most importantly, in both of these cases, vigilance regarding the establishment of a biochemical diagnosis, iodine pretreatment for thyroid uptake blockade prior to ^{123}I-mIBG scans, and consideration of ETT in the differential diagnosis of a hypervascular mediastinal mass with imaging modalities to differentiate between ETT and paraganglioma such as DOTATATE PET/CT or I-123 scan, would in all likelihood have avoided these unnecessary surgeries.

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Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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