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Pitfalls in the Diagnostic Evaluation of Pheochromocytomas

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Abstract

Pheochromocytomas and paragangliomas (PPGLs), rare neuroendocrine tumors arising from chromaffin cells, present a significant diagnostic challenge due to their clinical rarity and polymorphic symptomatology. The clinical cases demonstrate the importance of an integrated approach that combines clinical assessment, biochemical testing, and imaging to distinguish PPGLs from mimicking conditions, such as obstructive sleep apnea and interfering medication effects, which can lead to false-positive biochemical results. Although a rare condition, false-negative metanephrine levels can occur in pheochromocytomas, but imaging findings can give some clues and increase suspicion for a pheochromocytoma diagnosis. This expert endocrine consult underscores the critical role of evaluating preanalytical conditions and pretest probability in the biochemical diagnosis of PPGLs. Moreover, a careful differentiation of PPGLs from similar conditions and careful selection and interpretation of diagnostic tests, with focus on understanding and reducing false positives to enhance diagnostic accuracy and patient outcomes, is crucial.

Key Words: pheochromocytomas, paragangliomas, diagnosis, pitfalls, false-positive

Abbreviations: ^{131}I-MIBG, metaiodinebenzylguanidine labeled with iodine 131; BMI, body mass index; CPAP, continuous positive airway pressure; CT, computed tomography; HU, Hounsfield units; LC-MS/MS, liquid chromatography tandem mass spectrometry; MRI, magnetic resonance imaging; PPGL, pheochromocytomas and paraganglioma.

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine neoplasms arising from chromaffin cells within the adrenal medulla, known as pheochromocytomas, or from paravertebral sympathetic ganglia in thoracic and abdominal regions, as well as from cervical parasympathetic ganglia or the skull base, referred to as paragangliomas [1]. Pheochromocytomas account for approximately 80% to 85% of all PPGLs, with the remaining 15% to 20% being paragangliomas [2]. Distinction between these entities is solely predicated upon their anatomic location, as they are histopathologically indistinguishable [3]. Although the term "pheochromocytoma" has been entrenched in clinical vernacular, the World Health Organization has recently advocated for the nomenclature "adrenal paraganglioma" in an effort to standardize terminology [4].

PPGLs are noted for their clinical rarity, with a prevalence of less than 0.05% in the general population, rising to 0.2% to 0.6% among patients with hypertension [1]. Despite their infrequent occurrence, PPGLs carry a substantial burden of morbidity and mortality, predominantly due to cardiovascular complications and their propensity for metastatic disease [5, 6]. Metastatic lesions are detected in 15% to 20% of PPGL cases, denoted by metastatic dissemination to nonchromaffin tissues [7]. These tumors exhibit profound clinical heterogeneity and are frequently associated with hereditary syndromes, with up to 40% of cases linked to genetic disorders [8, 9]. Surgical excision remains the cornerstone of initial treatment, with the potential to achieve complete symptom resolution in PPGLs [1].

The diagnostic journey for pheochromocytomas is fraught with complexities, from nuanced clinical presentations to the intricacies of biochemical and imaging assessments. The rarity of PPGLs juxtaposed with the polymorphic nature of their symptoms often leads to misdiagnosis or significant delays in proper identification of the disease, thereby exacerbating patient morbidity [10]. Moreover, the diagnostic overlap with more prevalent conditions masks these neoplasms in clinical suspicion, culminating in a conundrum for the unwary clinician. As we venture further into the subtleties of diagnostic criteria, it becomes evident that a comprehensive and multifaceted approach is essential for an accurate detection. This article seeks to dissect these diagnostic intricacies, elucidate the common pitfalls encountered, and propose methodological enhancements to refine the diagnostic algorithm. By amplifying our understanding of these challenges and updating our diagnostic strategies, we aspire to improve patient outcomes and bridge the gap between initial presentation and definitive treatment.

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Case 1

A 58-year-old female patient was referred to an endocrinologist due to an incidental finding of a 1.8-cm mass in the right adrenal gland during abdominal computed tomography (CT) performed to investigate abdominal pain. Her medical history included refractory hypertension diagnosed at the age of 27, accompanied by hypertensive retinopathy, type 2 diabetes, dyslipidemia, grade 2 obesity, and severe obstructive sleep apnea (apnea–hypopnea index of 61.6/hour). She has been irregularly using continuous positive airway pressure (CPAP) therapy at night. The patient also experienced an acute myocardial infarction in 2019. Current medications were as follows: carvedilol 50 mg every 12 hours, chlorthalidone 25 mg daily, olmesartan 40 mg daily, amlodipine 10 mg daily, spironolactone 50 mg daily, clonidine 0.2 mg every 8 hours, hydralazine 50 mg every 6 hours, acetylsalicylic acid 100 mg daily, atorvastatin 80 mg daily, and metformin XR 1000 mg daily. At physical examination, weight was 92 kg, body mass index (BMI) 37 kg/m^2, blood pressure 150 × 90 mmHg, heart rate 64 bpm. No other signs of Cushing syndrome were noted. Abdominal CT revealed an undetermined right adrenal nodule measuring 1.8 × 1.2 cm with 18 Hounsfield units (HU) in the precontrast phase with arterial phase peak enhancement of 117 HU and an absolute washout of 65% (Fig. 1A). A slight nodular thickening up to 1.4 × 0.8 cm (−4 HU) in the left adrenal gland was suggestive of an adenoma (Fig. 1B).

Hormone evaluation showed a slight elevation in plasma normetanephrine (1.3 nmol/L) at recumbent position for 30 minutes before sampling and measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). Cortisol after a 1-mg dexamethasone overnight test was 2.3 µg/dL (Table 1). Due to the refractory hypertension, stopping interfering antihypertensive medications to rule out primary aldosteronism was not possible. A clonidine suppression test was indicated to investigate pheochromocytoma because this patient had an undetermined adrenal nodule (18 HU), high arterial phase peak enhancement (117 HU), and plasma normetanephrine between 1.5 and 2× the upper limit of normal range in 2 different measurements. Pheochromocytoma is excluded if there is a greater than 40% drop and normetanephrine is less than 80% of the upper limit of normal level for age after 180 minutes of clonidine with a sensitivity of 94% and a specificity of 97% [11]. The clonidine suppression test yielded a 25% reduction in plasma normetanephrine levels, indicating the biochemical diagnosis of pheochromocytoma (Table 2).

Case 2

A 47-year-old woman with type 1 neurofibromatosis was referred to the endocrinologist to investigate pheochromocytoma. She had no adrenergic symptoms and ambulatory blood pressure monitoring showed normal blood pressure. Biochemical and imaging investigation for pheochromocytoma was previously requested by her cardiologist. Plasma norepinephrine levels were 814.6 pg/mL (<460 pg/mL), epinephrine 19.7 pg/mL (<90 pg/mL), and dopamine <15 pg/mL. Plasma normetanephrines were elevated (1.2 nmol/L; 97.5th percentile for age 0.689 nmol/L) and metanephrines were 0.3 nmol/L (97.5th percentile for age 0.324 nmol/L) measured by LC-MS/MS (Table 2). She was using only zolpidem 10 mg/day for insomnia. Adrenals were normal at abdominal CT. Metaiodinebenzylguanidine labeled with iodine 131 (^{131}I-MIBG) scintigraphy was negative. Cutaneous neurofibromas had already been resected. At physical examination, her weight was 69.6 kg, BMI 29.2 kg/m^2, blood pressure 120 × 80 mmHg, and heart rate 88 bpm.

Case 3

A 5-cm right adrenal mass was incidentally discovered in a 52-year-old woman with nephrolithiasis. She had a previous diagnosis of hypertension at 25 years of age and a positive familial history of early hypertension. The patient underwent bilateral oophorectomy and hysterectomy without intraoperative and postoperative complications 10 years previously. She was taking losartan 50 mg every 12 hours and chlorthalidone 25 mg/day. At physical examination, her weight was 65.6 kg, BMI 25.6 kg/m^2, blood pressure 150 × 90 mmHg, and heart rate 96 bpm.

Abdominal CT revealed a right adrenal nodule measuring 5.2 × 4.0 cm with 34 HU in the precontrast phase with arterial phase peak enhancement of 122 HU and an absolute washout of 75% (Fig. 1C). Hormone evaluation showed normal plasma normetanephrine and metanephrine levels for age reference interval measured by LC-MS/MS. Cortisol after the 1-mg dexamethasone overnight test was 1.7 µg/dL (Table 1). Hormone work-up was negative and laparoscopic resection of the right adrenal mass was indicated.

Clinical Presentation and Diagnosis

The diagnosis of PPGL is typically suggested by 1 of 3 scenarios: (1) clinical suspicion, incidental adrenal lesions, or screening after the identification of an allelic variant pathogenic/likely pathogenic in a susceptibility gene for PPGL [6]. Diagnosis via incidental lesions and genetic screening of asymptomatic carriers have increased in recent years, possibly representing up to half to two-thirds of patients diagnosed with PPGLs [12].

Among symptomatic patients, hypertension is the most striking presentation, occurring in paroxysms or as a sustained condition [7]. The classic presentation consists of adrenergic paroxysms due to sudden tumoral catecholamine release, with the triad being composed of headache, sweating, and tachycardia. Adrenergic paroxysms can occur spontaneously or be provoked by medications (ephedrine, amphetamines, metoclopramide, opioids, antidepressants, and anesthetics), physical exertion, increased abdominal pressure, stress, or certain foods [13]. They are present in approximately 50% of cases, while the remainder of patients exhibit sustained hypertension or, less frequently (10-15% of cases), normal blood pressure [7, 12, 14]. Other less common signs and symptoms in PPGL patients include weight loss, headache, constipation, tremors, pallor, blood pressure lability, and flushing [12]. None of the signs or symptoms, alone or grouped, are sufficiently sensitive or specific to allow firm diagnosis simply on clinical grounds.

The extensive clinical diversity of PPGLs is elucidated by the quantity, frequency, and type of catecholamine released by the tumor [15]. The catecholamines encompass dopamine, norepinephrine, and epinephrine (Fig. 2). All are derived from tyrosine and are metabolized into 3-methoxytyramine, normetanephrine, and metanephrine, respectively. Approximately 50% of all pheochromocytomas synthesize and release a blend of epinephrine and norepinephrine, whereas the majority of the remaining tumors, particularly sympathetic paragangliomas, predominantly secrete norepinephrine [16]. This

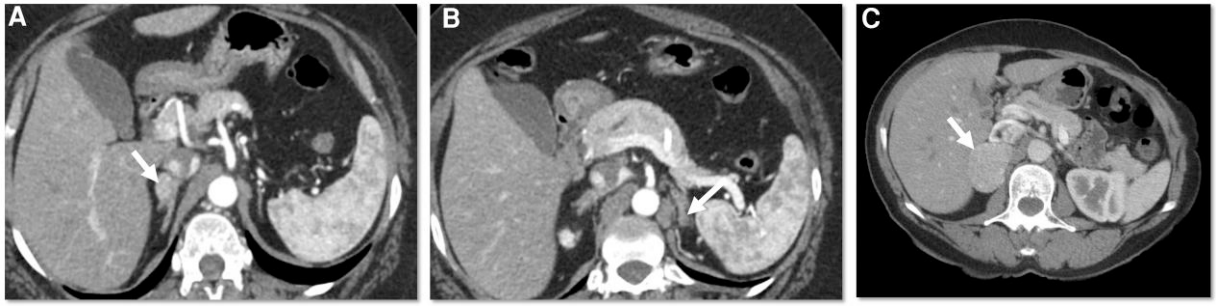

Figure 1. (A, B) Case 1. (A) Abdominal CT revealing an undetermined right adrenal nodule measuring 1.8 × 1.2 cm (white arrow) with 18 Hounsfield unit (HU) in the precontrast phase with arterial phase peak enhancement of 117 HU and an absolute washout of 65%. (B) Slight nodular thickening up to 1.4 × 0.8 cm (−4 HU) in the left adrenal gland (white arrow), suggestive of adenoma. (C) Case 3. Abdominal CT revealing a right adrenal nodule measuring 5.2 × 4.0 cm (white arrow) with 34 HU in the precontrast phase with arterial phase peak enhancement of 122 HU and an absolute washout of 75%.

variation in catecholamine production is contingent on the expression of phenylethanolamine-N-methyltransferase, the enzyme responsible for the conversion of norepinephrine to epinephrine. A subset of tumors, exhibiting minimal or no expression of dopamine-β-hydroxylase (the enzyme that catalyzes the transformation of dopamine to norepinephrine) may secrete mixtures of dopamine and norepinephrine or, in certain cases of paragangliomas, solely dopamine. In the clinical context, patients with tumors secreting adrenaline typically exhibit episodic manifestations, though intervals of normotension and asymptomatic phases are not uncommon [7]. In contrast, those with tumors primarily secreting noradrenaline frequently present with a clinical picture resembling essential hypertension, often exhibiting a more subclinical presentation. The chronic elevation of noradrenaline can lead to adrenoceptor desensitization, further attenuating clinical symptoms and potentially normalizing blood pressure [16].

Tumors exclusively secreting dopamine are relatively rare and reflect an absence of dopamine β-hydroxylase activity. Dopamine levels in these cases can be quantified through plasma assessments or by analyzing its metabolite 3-methoxytyramine in plasma or urine [17]. Elevated levels of 3-methoxytyramine may indicate malignancy. Elevated plasma dopamine may induce vasodilation and inhibit the release of noradrenaline, consequently moderating the hemodynamic effects associated with elevated noradrenaline levels [7]. Most paragangliomas that do not produce catecholamines (noncatecholamine-producing paragangliomas) originate from the parasympathetic nervous system, typically situated in the head or neck [16]. The absence of catecholamine secretion in these PPGLs may be attributed to their conversion into inactive metabolites or a deficiency in synthesis, frequently due to abnormalities in tyrosine hydroxylase function. However, the existing literature on this subject remains limited and requires further exploration and documentation.

A regular follow-up of genetically affected relatives will permit a diagnosis of PPGLs at an early stage when the tumor is still small, and the clinical picture is mild or even silent. In autopsy studies, the mean prevalence of adrenal masses was found to be approximately 6% [18]. This observation appears to be corroborated by the approximately 5% prevalence of adrenal masses detected through CT [6, 15, 19, 20].

Biochemical Diagnosis

The first step for a symptomatic patient suspected for PPGL or incidentally adrenal lesion is the proof of excessive release of catecholamines or their metabolites. The initial investigation for suspected PPGLs should be conducted through measurement of free plasma metanephrines or fractionated 24-hour urinary metanephrines determined by LC-MS/MS [1, 13]. Free plasma metanephrines or fractionated urinary metanephrines have superior diagnostic accuracy than fractionated catecholamines (epinephrine, norepinephrine, and dopamine) and vanillylmandelic acid (VMA) in urine, due to the continuous intratumoral metabolization of catecholamines [21]. Historically, urinary VMA measurements were the predominant diagnostic tool for PPGLs. However, urinary VMA application has significantly declined with the advent of newer and more precise diagnostic methods [15]. In a comprehensive study involving 214 patients with PPGLs, the diagnostic sensitivity of urinary vanillylmandelic acid was 77% for patients with sporadic PPGLs, which markedly decreased to 46% in those with hereditary forms of the disease [22].

The initial identification of the diagnostic utility of plasma free metanephrines in detecting PPGLs was reported in 1995 [15, 23]. This revelation has since been corroborated by a multitude of studies, which have consistently demonstrated the superior diagnostic performance of LC with electrochemical detection or LC-MS/MS in measuring plasma free or urinary metanephrines [23, 24]. These studies have reported sensitivities ranging from 95% to 100% and specificities between 89% and 100% [15, 23]. In contemporary clinical practice, LC-MS/MS has become the predominant methodology adopted by most laboratories for these measurements [1]. Despite the known limitations in accuracy, some laboratories continue to utilize commercially available immunoassay methods for the quantification of plasma free metanephrines.

The sensitivity of free plasma metanephrines and normetanephrines is higher than that of their urinary counterparts (98% vs 93%), but both possess similar specificities (94%) [25]. In patients with adrenal incidentaloma or carriers of susceptibility gene mutations, free plasma metanephrines demonstrate greater accuracy and sensitivity than urinary metanephrines [26]. In contrast, measurement of urinary fractionated catecholamines (epinephrine, norepinephrine, and dopamine) is less sensitive, but clearly elevated values (>2 times the upper limit of the normal range) indicate the diagnosis of PPGLs [6]. The preferential production of normetanephrine over norepinephrine in chromaffin cells, as opposed to sympathetic nerves, plays a pivotal role in enhancing the diagnostic value of this metabolite compared with its precursor amine in the detection of PPGLs. However, it is crucial to acknowledge

Table 1. Hormone work-up of the 3 clinical cases

Cases	1	2	3
Metanephrine (nmol/L)[a]	0.3 (<0.375)	0.3 (<0.324)	<0.2 (<0.375)
Normetanephrine (nmol/L)[a]	1.3 (<0.747)	1.2 (<0.6889)	0.6 (<0.747)
Renin (4.4-46 μIU/mL)	36.8		15.4
Aldosterone (ng/dL)	9.9		6.8
ACTH (pg/mL)	15.7		28
Cortisol (μg/dL)	7.0		11.2
Cortisol after overnight 1 mg dexamethasone (μg/dL)	2.3		1.7
DHEA sulfate (ng/mL)	1152 (189-2050)		872 (189-2050)

Abbreviations: ACTH, adrenocorticotropin; DHEA, dehydroepiandrosterone.
[a]97.5th percentile for age.

that approximately 75% of normetanephrine originates from the sympathoneural release of norepinephrine, a factor which is essential for understanding the etiology of false-positive results in plasma or urinary normetanephrine [15].

Nonfunctional PPGLs are characterized by their lack of catecholamine synthesis and secretion. These tumors predominantly occur within the head and neck region and, less frequently, within the upper or anterior mediastinum [27]. These tumors tend to be diagnosed at larger sizes, frequently as a result of mass effects or incidental findings during imaging procedures [16]. The absence of catecholamine secretion and metabolism in these neoplasms is typically due to a deficiency in catecholamine synthesis, likely stemming from the lack of tyrosine hydroxylase activity rather than an impairment in the storage or exocytosis of these neurotransmitters. Given that the aggregate levels of plasma free metanephrines correlate with tumor size, it may be feasible to discern nonfunctional tumors from those that are merely biochemically negative [7]. Nonfunctional tumors are thus delineated by the absence of biochemical evidence of catecholamine excess and by a mean tumor diameter exceeding 2 cm [16]. Consequently, the designation "nonfunctional", assigned to patients with PPGLs who exhibit negative biochemical test results for plasma free metanephrines, was demonstrated in 2% (5 out of 236 cases) of PPGLs [25].

A small minority of head and neck paragangliomas, approximately 3% to 4%, are known to produce norepinephrine. However, a significant portion, up to one-third, may synthesize dopamine. Inclusion of measurements of free methoxytyramine in the plasma panel is useful for detecting dopamine-producing tumors, whereas measurements of urinary dopamine or methoxytyramine are less useful since the analytes in urine are largely derived from sources independent of the circulating amines [15, 28]. The plasma concentrations of methoxytyramine have been observed to be markedly higher in patients who have not observed fasting than in those who have maintained an overnight fast [29]. Therefore, to ensure the reliability of methoxytyramine measurements, it is recommended that patients adhere to a strict overnight fasting regimen, which should be sustained until the time of blood collection in the following morning.

Anatomical Diagnosis

When biochemical testing yields suggestive results, it is advisable to proceed with cross-sectional imaging using contrast-enhanced CT or magnetic resonance imaging (MRI) of the entire abdomen [1, 13]. Ultrasound is generally not recommended owing to its limited sensitivity in detecting PPGLs [6, 19]. Predominantly, extra-adrenal catecholamine-secreting tumors are situated in the retroperitoneum, as opposed to the pelvis or thorax. Pheochromocytomas can present with a range of radiological characteristics including homogeneity or heterogeneity, solid or cystic composition, or the presence of necrosis and calcification [30]. Owing to their broad spectrum of radiological features, PPGLs lesions may be erroneously identified as adrenal cortical carcinoma, cystic infectious lesions, or metastatic lesions, and, albeit less frequently, adrenal lipid-poor adenomas and retroperitoneal lymphomas. Consequently, the measurement of metanephrines plays a crucial role in the presumptive diagnosis of pheochromocytomas [26].

Table 2. Clonidine suppression test indicated to investigate pheochromocytoma in case 1 with undetermined adrenal nodule (18 HU), high arterial phase peak enhancement (117 HU), and plasma normetanephrine between 1.5 and 2× the upper limit of normal range

Clonidine suppression test (0.3 mg)	Baseline	180 minutes
Plasma metanephrine (<0.375 nmol/L)[a]	0.3	0.3
Plasma normetanephrine (<0.747 nmol/L)[a]	1.2	0.9[b]

[a]97.5th percentile for age (50-59 years old).
[b]Pheochromocytoma is excluded if there is a greater than 40% drop and normetanephrine is less than 80% of the upper limit of normal level for age.

Performing contrast-enhanced CT is usually the first method to locate the PPGLs. The nonionic contrast media is considered safe in patients who have not undergone adrenergic receptor blockade [31, 32]. In a comprehensive multicenter retrospective analysis focused on assessing the radiologic characteristics of pheochromocytomas via CT imaging, only 0.5% of the cases, precisely 2 cases, exhibited unenhanced attenuation at exactly 10 HU [32]. From these observations, the authors recommended that it is not necessary to perform biochemical testing for pheochromocytomas in adrenal incidentalomas with unenhanced attenuation ≤10 HU. Nonetheless, they caution that reliance solely on contrast washout metrics for the exclusion of pheochromocytomas is not sufficiently reliable. In a meta-analysis, Woo and colleagues corroborate the aforementioned caution regarding the diagnostic efficacy of washout metrics [33]. A significant proportion (35%) of pheochromocytomas met the criteria

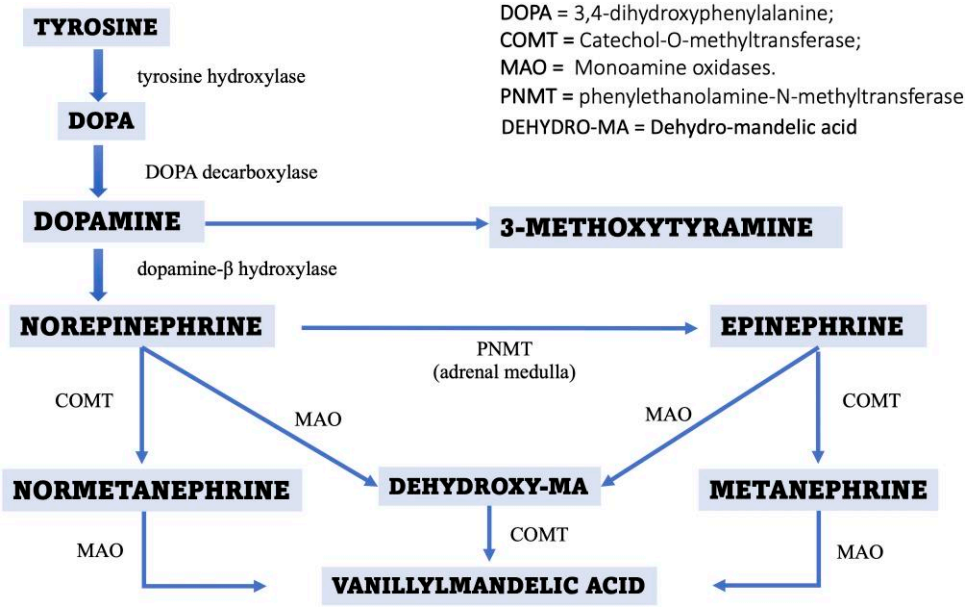

Figure 2. Pathway of catecholamine biosynthesis and metabolism of the most relevant metabolites for biochemical diagnosis of pheochromocytomas and paragangliomas.

for adrenal adenoma when using adrenal washout CT [33]. Although pheochromocytomas show a high peak enhancement in early arterial phase, a cut-off of 100 HU had only a moderate sensitivity (63.6%) and a high specificity (100%) to differentiate pheochromocytoma from other lipid-poor adrenal lesions [34].

MRI is the preferred imaging modality for patients with metastatic disease, head and neck paragangliomas, iodine contrast allergy, or those requiring reduced radiation exposure, such as children, pregnant women, and individuals with germline genetic defects [13]. The utility of high signal intensity on T2-weighted MRI images in localizing pheochromocytomas, although less common than previously believed, can still be valuable [7, 11]. Head and neck paragangliomas typically shows slowly enlarging masses, often manifesting as carotid-body tumors and vagal tumors, or as conductive hearing loss and pulsatile tinnitus in cases of jugulotympanic paragangliomas [6, 35]. The tumor's low-signal voids, typical of paragangliomas, present a "salt-and-pepper" pattern on MRI spin echo imaging sequences [36].

Nuclear imaging serves as a valuable adjunct to morphological imaging in the diagnosis and staging of diseases [20]. It has the added advantage in accurately predicting tumor response to eventual treatment with radiolabeled nuclear analogs in patients with avidity for the tracer. Radiopharmaceuticals, distinct from contrast agents, offer specificity to the PPGL lesions, thus facilitating the detection of diminutive lesions in scenarios of multifocal or metastatic disease [37]. These agents yield critical molecular insights, exemplified by compounds like ^{131}I- MIBG, ^{18}F-FDOPA, and somatostatin receptor positron emission tomography, though it is notable that ^{18}F-FDG lacks this specificity [38].

MIBG functions as a functional analog of norepinephrine, being incorporated into secretory granules for storage and subsequent exocytosis [19]. Recent research, including a broader spectrum of paraganglioma cases, indicates a generally lower sensitivity of MIBG in detecting these tumors, particularly in hereditary undifferentiated pheochromocytoma or paraganglioma [37]. Typically, the sensitivity of ^{131}I-MIBG is greater for pheochromocytoma (88%) than for paraganglioma (67%) [30]. Notably, MIBG sensitivity is markedly reduced in patients with *SDHx* gene mutations [39, 40]. With the advent of newer radiopharmaceuticals, the once central role of radiolabeled MIBG in pheochromocytoma/paraganglioma imaging has shifted towards a screening tool for ^{131}I-MIBG therapy [41].

^{68}Ga-DOTA-SSA studies have shown excellent lesion-based sensitivity in detecting PPGLs, often more than 92% [30]. A metanalysis comparing the sensitivity of ^{18}F-FDG and ^{68}Ga-DOTA-SSA found that the sensitivity of ^{68}Ga-DOTA-SSA (95%) was superior to that of ^{18}F-FDG (85%) [30]. An additional metanalysis demonstrated that the sensitivity of ^{68}Ga-DOTA-SSA (93%) was superior to ^{18}F-FDOPA (80%), ^{18}F-FDG (74%), and ^{123}I/^{131}I-MIBG (38%) [42]. Overall, ^{68}Ga-DOTATATE should be considered the tracer of choice for evaluating metastatic pheochromocytoma, metastatic paraganglioma, *SDH*x mutant carriers, and head and neck paragangliomas [7, 43]. An exception is pheochromocytoma or paraganglioma associated with polycythemia, *MAX* mutations, or apparently sporadic pheochromocytoma, for which ^{18}F-FDOPA may be preferable [20, 41]. Genetics of PPGLs translates into 3 main clusters with distinct tumor locations, biochemical features, tumor receptor characteristics, and risk of metastatic disease. Nowadays, the choice of radionuclides to diagnostic work-up and treatment is based on the germline genotype [44].

Pretest Probability

The pursuit of PPGLs is frequent, yet their actual detection remains a rarity. This leads to a scenario where the pretest prevalence of PPGLs is notably low, and the incidence of false-positive results in biochemical assessments is correspondingly high [10, 45]. Contrasting with singular, subjective indications, the presence of 3 or more symptoms indicative of catecholamine excess (including hyperhidrosis, palpitations, pallor, tremor, or nausea), in conjunction with a BMI below

25 kg/m^2 and a heart rate exceeding 85 beats per minute, markedly increases (by 7.5 times) the likelihood of an underlying PPGL [12].

In addition to identifying these neoplasms in individuals presenting with overt signs and symptoms of catecholamine excess, there is a growing trend of detecting these tumors incidentally [1, 6]. This often occurs during anatomical imaging procedures conducted for reasons unrelated to the primary clinical suspicion of PPGL. Parallel to these developments, the acknowledgment of hereditary factors in the etiology of PPGLs has led to their increased identification within surveillance programs [37]. These programs specifically target individuals harboring germline pathogenic variants of genes associated with tumor susceptibility, intensifying the focus on preemptive testing. Within this cohort, a notable proportion, approximately 20% to 50%, may present as normotensive and/or entirely asymptomatic [15]. Yet, it is not uncommon for the manifestations of catecholamine excess to be overlooked in others within this group. These tumors, when detected via surveillance protocols, are typically smaller and may secrete relatively modest quantities of catecholamines. Consequently, this can result in minimal or even nonelevated levels of the relevant biomarkers within established reference intervals. Nonetheless, it is imperative to note that the pretest prevalence of PPGL in such patients is higher than in those evaluated primarily based on clinical signs and symptoms.

While only 4% of patients who presented with suggestive signs and symptoms were finally diagnosed with PPGL, detection rates were 42% in patients with a history of a previously resected PPGL, 40% in case of genetic predisposition, and 28% in adrenal incidentalomas [11]. Therefore, the pretest risk of harboring an actual PPGL can be summarized as high in patients with a prior history of PPGL, carriers of pathogenic variants in susceptibility genes, and those with adrenal incidentalomas [15]. Conversely, patients presenting solely with adrenergic clinical manifestations, particularly those with a lower point score, are deemed to have a low pretest risk [7]. This risk stratification may aid in the appraisal of biochemical or imaging examinations that present with conflicting results.

False-Positive Situations

In clinical settings, the occurrence of false-positive results in biochemical testing for PPGLs is relatively common [46]. When considering unselected patient populations, the incidence of false-positive results for plasma free or urinary fractionated metanephrines can be around 20% to 25% [29, 47]. While concurrent elevations in both metanephrines and normetanephrines are uncommon, isolated increases in normetanephrines, reaching levels up to 2 to 3 times the upper reference limit, are more frequently observed [48].

Preanalytical considerations, such as the method of blood collection (immediate needle stick vs an indwelling catheter), abstaining from smoking, physical activity, and avoiding interfering medications, along with establishing intravenous access 30 minutes before the blood draw, are critical factors to ensure accurate results [1, 15, 49] (Fig. 3). Strictly controlled preanalytical conditions, including supine positioning and age-adjusted plasma measurements, demonstrates that less than 8% of patients require additional testing, thereby reducing the necessity for most confirmatory tests for PPGLs [49]. In previous reports where blood sampling was conducted with subjects in a seated posture, a reduced diagnostic specificity (approximately 76% to 85%) was observed, notwithstanding the preservation of a notably high diagnostic sensitivity (ranging from 93% to 97%) was observed [15]. The incidence of false-positive results for plasma methoxytyramine is notably higher in nonfasting patients than in those who observe an overnight fast. Dopamine, which significantly influences measured levels of itself and its metabolites, is abundantly present in bananas, and is also found in various other fruits, vegetables, and assorted foods [15, 50].

In the diagnostic investigation of PPGLs, it is crucial to meticulously assess the patient's medication history, as various drugs can significantly influence biochemical test results, leading to potential misdiagnoses. Drug interactions contribute to approximately 20% of all false-positive biochemical test results for PPGLs [47]. Tricyclic antidepressants, known for blocking norepinephrine reuptake, have been consistently linked to elevated false-positive rates for plasma and urinary normetanephrine [15, 50]. Phenoxybenzamine, identified as a nonselective alpha-adrenoceptor antagonist, similarly inhibits norepinephrine uptake. Notably, these 2 drug types were responsible for 41% to 45% of the increased levels of norepinephrine and normetanephrine observed in patients who did not have a PPGL, as previously documented [51]. False-positive results remain a problem in patients taking serotonin–norepinephrine (dual) reuptake inhibitors. Plasma concentrations of normetanephrine in patients taking serotonin–norepinephrine reuptake inhibitors were 35% higher according to Schürfeld et al [51]. Similar to other interfering medications, dual reuptake inhibitors, such as venlafaxine and duloxetine, cause false-positive results with mild elevations in metanephrine levels. Previous case reports have demonstrated that venlafaxine can result in significantly false elevated normetanephrine levels, exceeding 4 times the upper reference limit [52, 53]. In contrast, selective serotonin reuptake inhibitors did not increase plasma concentrations of catecholamine metabolites [51].

Unlike phenoxybenzamine, selective α_1-adrenoceptor blockers, including doxazosin, terazosin, and prazosin, do not elevate false-positive rates for plasma norepinephrine and normetanephrine [15]. However, these medications are associated with a 4-fold increase in false-positive rates for urinary norepinephrine, while having no significant impact on urinary metanephrine levels [48]. Other antihypertensive drugs, such as calcium channel blockers, diuretics, and β-adrenoceptor blockers, are not associated with false-positive results, and their withdrawal before testing is not necessary.

Atypical antipsychotics, including quetiapine, clozapine, and risperidone, represent other group of psychiatric medications known to cause false-positive results for norepinephrine and normetanephrine [15]. These agents act as antagonists on dopaminergic, adrenergic, and serotonergic receptors. The precise mechanism by which this drug class leads to increased norepinephrine secretion remains unclear, but antagonism at α_2-adrenergic and D_2 dopaminergic receptors might contribute. Zolpidem is a $GABA_A$ receptor agonist of the imidazopyridine class, primarily used for short-term treatment of sleeping problems. In our practice, zolpidem was associated with false-positive normetanephrine levels, but the mechanism to explain this effect is not known.

Finally, recreational drugs such as cocaine, which inhibits norepinephrine reuptake, amphetamines, attention-deficit

Adrenal/Retroperitoneal Lesions That May Mimic a Pheochromocytoma or Paraganglioma (PPGL):

- Adrenal cortical carcinoma
- Cystic infectious lesions
- Metastatic lesions
- Lipid-Poor Adenoma
- Retroperitoneal lymphoma

Preanalytical conditions:

- Check for use of interfering medications / recreational drugs / supplements
- Check blood sampling*
- Check for use of age-specific reference intervals
- Consider type of assay **
- In case of isolated MTY elevation: check renal function and fasting state at blood withdrawal.

* After 30-minute rest in the supine position

**Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

False-negative conditions:

- Small size tumor (especially < 1 cm)
- Dopamine isolate producing tumor (rare)
- Non-functional tumor (rare)
- Non sensitive test performed (catecholamines)

Figure 3. Flowchart pointing out some important scenarios and conditions to be evaluated during the investigation of suspicious PPGLs.

hyperactivity disorder treatments with methylphenidate, and antiobesity drugs such as phentermine, all known to stimulate catecholamine release, may contribute to false-positive results. L-DOPA, frequently prescribed for Parkinson disease, can also lead to false elevations of 3-methoxytyramine and metanephrines. Similarly, sympathomimetics including ephedrine and pseudoephedrine enhance catecholamine production along with their metabolites [50]. Additionally, withdrawal from sedatives such as benzodiazepines, opioids, clonidine, and alcohol can elevate sympathetic activity, further leading to false-positive results. The medications that interfere with the diagnosis of PPGLs and their respective implicated mechanisms are summarized in Table 3. Prior to the sampling of metanephrines, it is recommended for patients to discontinue all medications that could potentially influence urinary or plasma metanephrines levels for at least one month [1]. The consumption of beverages containing caffeine within the last 24 hours should be avoided, particularly in situations where tests have shown previously mild elevations [15, 54].

In chronic kidney disease, the biochemical evaluation for PPGLs is rendered complex due to a confluence of factors, including sympathoadrenal activation, the accrual of interferents in the bloodstream, and altered circulatory and renal clearance dynamics [15]. The utility of urinary metanephrines measurements is compromised in chronic kidney disease due to the effect of renal impairment on catecholamine and metanephrine excretion, although this impact is less pronounced in cases of mild to moderate renal dysfunction [55]. Plasma free metanephrines, predominantly cleared via extraneuronal mechanisms similarly to catecholamines and with minimal

Table 3. Medications that interfere with the biochemical diagnosis of pheochromocytomas and paragangliomas and their respective implicated mechanisms

Medication class	Examples	Impact on catecholamines
Tricyclic antidepressants	Amitriptyline, nortriptyline	Inhibit reuptake of norepinephrine and serotonin, potentially increasing catecholamine levels
Nonselective α-adrenoceptor antagonist	Phenoxybenzamine	Inhibits norepinephrine uptake
Serotonin–norepinephrine reuptake inhibitors	Venlafaxine, desvenlafaxine, duloxetine	Inhibit reuptake of serotonin and norepinephrine, potentially raising catecholamine levels
Atypical antipsychotics	Quetiapine, clozapine, and risperidone	Adrenergic activity of some antipsychotics may affect catecholamine levels
Monoamine oxidase inhibitors	Phenelzine, tranylcypromine	Inhibit monoamine oxidase, an enzyme involved in catecholamine breakdown, potentially increasing catecholamine levels
Sympathomimetics	Pseudoephedrine, albuterol, phentermine, caffeine, and nicotine	Directly stimulate adrenergic receptors or increase catecholamine release, raising catecholamine levels
Anti-Parkinson	Levodopa	Precursor to dopamine, can increase catecholamine synthesis
Amphetamines	Methylphenidate, dextroamphetamine	Increase release and inhibit reuptake of catecholamines
Opioids	Oxycodone, hydrocodone, codeine, morphine	May indirectly influence catecholamine levels through central nervous system mechanisms
Agonist of $GABA_A$ receptors	Zolpidem	unknown
Cocaine and derivatives		Inhibit reuptake of catecholamines, increasing their levels
Alcohol or sedative withdrawal		Withdrawal can lead to increased sympathetic activity and catecholamine release
Clonidine withdrawal		Rebound increase in catecholamines after discontinuation
β-Blockers (nonselective)	Atenolol, propranolol	Inhibit catecholamine breakdown and metabolism, potentially leading to increased levels

renal involvement, emerge as a more reliable indicator in patients with severe renal impairment or end-stage renal disease [15, 19]. In the setting of hemodialysis, re-evaluating plasma metanephrines levels postdialysis and from dialysis shunt samples is recommended [15]. The 97.5th percentile for normetanephrine and metanephrine levels has been established in patients with stage III and stage IV/hemodialysis chronic kidney disease [56].

In the acute clinical setting, accurately diagnosing a PPGL as the underlying cause of a catecholamine-induced hypertensive crisis presents significant challenges [57]. This condition is often compounded by various comorbidities and acute stressors such as panic disorders, hypoglycemia, ischemic heart disease, or circumstances surrounding emergency department admission, which can interfere with biochemical evaluations and potentially lead to misdiagnosis. Severe acute and chronic illnesses are itself frequently accompanied by sympathoadrenal activation as a part of the body's homeostatic response [50]. These acute states can cause mild to significant increases in plasma and urinary metanephrines, especially normetanephrine [15]. Consequently, biochemical testing for catecholamine excess in these scenarios is less likely to produce interpretable results [58].

Obstructive sleep apnea is a very prevalent and underdiagnosed disease associated with a high cardiovascular morbimortality [59]. The pathophysiological mechanisms of the development of arterial hypertension in patients with obstructive sleep apnea include a disorder of the autonomic nervous system with excessive sympathetic activation due to intermittent hypoxia during the night [60]. Obstructive sleep apnea leads to increased nocturnal catecholamine release and a higher rate of false-positive test for norepinephrine and normetanephrine.

Given the widespread occurrence of obesity and obstructive sleep apnea, distinguishing between the latter condition and PPGLs has become a prevalent and challenging scenario. Interestingly, CPAP therapy improved the dysregulation of the autonomic nervous system [61] and normalized elevated urinary normetanephrine levels [62]. Recently, King et al [63] demonstrated that plasma normetanephrines are less likely to yield false-positive results for the diagnosis of PPGL than 24-hour urinary normetanephrines in patients with obstructive sleep apnea.

Additional factors including BMI, gender, time of sample collection during the day, and menstrual cycle phase seem to have a negligible impact on the biochemical diagnosis of PPGLs [50].

Differential Diagnosis

In the clinical diagnostic landscape, the identification of pheochromocytoma stands as a complex endeavor, demanding careful differentiation from principal alternative diagnoses. This spectrum includes conditions that mimic adrenergic responses, such as hypoglycemia, climacteric hot flashes, other secretory gastrointestinal neuroendocrine neoplasms, and psychiatric and cardiovascular disorders, each potentially presenting with symptoms similar to those observed in PPGL presentation [64]. The differential diagnoses for PPGLs are comprehensively compiled and enumerated in Table 4. Anxiety crises and panic disorders are conditions that should frequently be considered in the assessment of patients presenting with symptoms of adrenergic paroxysms. Nevertheless, in instances of long-standing panic disorder that is resistant to medication, it is crucial to rule out the diagnosis of pheochromocytoma [13, 65]. This intricate diagnostic scenario

accentuates the necessity for a thorough and meticulous evaluative process to accurately diagnose PPGLs [13].

Pseudopheochromocytoma is an atypical medical condition that mirrors the clinical presentation of a true pheochromocytoma without the presence of a catecholamine-secreting tumor. Patients with pseudopheochromocytoma exhibit episodic hypertension, headaches, palpitations, and diaphoresis, the classic symptoms associated with pheochromocytoma, yet biochemical testing does not demonstrate elevated catecholamine levels as expected in true pheochromocytoma [66]. The precise pathophysiological mechanisms underlying this condition remain elusive and are believed to be multifactorial. There is a consensus that the aberrant regulation of the autonomic nervous system plays a central role, wherein sympathetic overactivity may arise independent of catecholamine-secreting tumors [67, 68]. In the elucidation of pseudopheochromocytoma pathophysiology, Sharabi et al provided evidence of an atypical catecholaminergic profile in these patients [66]. Their findings indicated that, compared with healthy controls, individuals with pseudopheochromocytoma did not exhibit elevated norepinephrine levels but did demonstrate significantly increased baseline plasma concentrations of epinephrine and metanephrines [66, 68]. This dysregulation may be intrinsically linked to psychological stressors, with some studies suggesting a higher prevalence of underlying psychiatric conditions such as anxiety or panic disorders among these patients [66].

The management of pseudopheochromocytoma is inherently challenging due to its symptomatic mimicry of pheochromocytoma and the lack of a definitive biochemical marker. The primary approach involves a thorough exclusion of a catecholamine-secreting tumor via comprehensive biochemical screening. Upon exclusion of pheochromocytoma, the focus shifts to the management of the episodic hypertension and associated symptoms [69]. Pharmacological interventions may include the use of antihypertensive agents, particularly those targeting the sympathetic nervous system, such as α-blockers or β-blockers [68, 69]. These medications can mitigate the hypertensive episodes and control the adrenergic symptoms. In contrast, conventional antihypertensive medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics often prove ineffective [68]. Additionally, a multidisciplinary approach involving psychological support and psychiatric care is important.

Table 4. Comprehensive differential diagnosis for pheochromocytomas and paragangliomas (PPGLs)

Differential Diagnosis	Description
Pseudopheochromocytoma	Hypertension and symptoms mimicking PPGL without actual tumor presence
Panic disorder/anxiety	Episodes of intense fear and discomfort potentially mimicking catecholamine excess symptoms
Hypoglycemia	Low blood sugar levels causing symptoms that can overlap with PPGL
Obstructive sleep apnea	Disorder characterized by pauses in breathing or periods of shallow breathing during sleep, leading to arterial hypertension and sympathetic activation
Menopausal hot flashes	Sudden feelings of warmth, which are usually most intense over the face, neck, and chest
Drug withdrawal syndromes	Symptoms arising from the cessation or reduction in the intake of addictive substances
Carcinoid syndrome	A set of symptoms associated with carcinoid tumors, especially flushing and diarrhea
Cardiovascular emergencies	Including ischemic heart disease, heart failure, postural orthostatic tachycardia syndrome, syncope, acute ischemic stroke
Acute baroreflex failure	A rare condition presenting as severe labile hypertension and orthostatic hypotension
Autonomic epilepsy	Seizures originating from the autonomic nervous system, presenting with various autonomic symptoms
Early dumping syndrome	A group of symptoms, typically gastrointestinal, that occur after eating, most commonly following gastric surgery
Acrodynia (mercury poisoning)	A symptom complex primarily affecting young children, involving pain and pink discoloration of the hands and feet
Factitious catecholamine administration	Administration of catecholamines leading to symptoms mimicking PPGL

False-Negative Situations

With rare exceptions, contemporary assays for plasma and urinary metanephrines exhibit exceptionally high sensitivity in diagnosing patients suspected of harboring PPGLs (Fig. 3). In a prospective study involving patients with and without PPGLs, it was observed that the immunoassay method yielded a significant number of false-negative results, failing to detect PPGLs in up to 25% of the cases [23]. In assessing the sensitivity of plasma free metanephrine measurements, currently considered the most sensitive diagnostic test, a recent prospective study reported a false-negative rate of 2.1% [25]. However, among the patients with false-negative results, none of the 5 individuals with false-negative outcomes for plasma free metanephrines and only 1 out of the 16 with false-negative results for urinary metabolites were evaluated on the basis of adrenergic signs and symptoms [15].

Small tumors or incipient recurrences might generate minimal levels of epinephrine and norepinephrine, leading to their nondetection. There is a positive correlation between the combined levels of plasma free metanephrines and tumor size, which can aid in distinguishing nonfunctional tumors from those that are merely biochemically inactive [21]. The lack of a biochemical signal was likely due to the small size of the tumors, rather than an absence of catecholamine production. Hence, carriers of a predisposition gene mutation for PPGL may present with a negative biochemical work-up [50]. Tumors identified during initial screening often exhibit a biochemical phenotype classified as indeterminate due to their small or microscopic tumor burden (less than 2 cm) or as nonfunctional in the context of larger tumors (greater than 2 cm). This distinction is based on the understanding

that a tumor size greater than 2 cm is consider sufficient to yield elevated metanephrine levels [16, 21, 45].

It has been observed that paragangliomas producing dopamine can be overlooked if only epinephrine, norepinephrine, and their metabolites are measured, or if the tumor rapidly metabolizes dopamine to methoxytyramine due to a highly active catechol-O-methyltransferase isoenzyme [15]. Consequently, methoxytyramine is considered a more effective marker for detecting dopamine-producing tumors [19, 70, 71]. Hypertension is not typically associated with dopamine-producing paragangliomas. Indeed, these tumors may present with hypotension and other atypical symptoms [7, 37, 50].

The Clonidine Suppression Test

The clonidine (central α_2-adrenoceptor agonist) suppression test leverages clonidine's capacity to inhibit noradrenaline release from normal adrenal glands, a response not observed in patients with PPGL tumors. This test is particularly valuable in distinguishing true PPGLs from other conditions that elevate catecholamines, like essential hypertension, stress, or certain drugs, especially in patients with borderline elevated noradrenaline or normetanephrine levels. It should be emphasized that this test is not indicated when only adrenaline and/or metanephrine are elevated [48]. Recently, an improved cut-off for plasma normetanephrine at 180 minutes after clonidine (instead of a suppression <40%) was established at 80% of the age-related upper limit of normal, resulting in a sensitivity of 94% and a specificity of 97% [11].

A critical point to be considered before performing the clonidine test is the concomitant use of norepinephrine reuptake blockers, which will interfere with clonidine action, not resulting in the reduction of plasma norepinephrine or normetanephrine [15, 19]. Therefore, clinicians should not perform the clonidine suppression test in patients taking norepinephrine uptake blockers or other interfering medications [15, 51]. Similarly, the accuracy of the clonidine suppression test can also be compromised if the underlying clinical conditions elevating catecholamines were not removed or treated.

Back to the Cases

Case 1

Alpha-blockade with doxazosin 4 mg was started and the patient underwent right adrenalectomy after 4 weeks. Doxazosin was stopped 12 hours before adrenalectomy and hemodynamic instability did not occur in the intraoperative period. Pathological examination revealed a Weiss score 0 adenoma with positive immunohistochemistry for CYP11B2 (aldosterone synthase). After adjustments in CPAP therapy (reduction of pressure and ramp settings), a significant improvement in the obstructive sleep apnea occurred and plasma normetanephrine normalized (0.7 nmol/L; 97.5th percentile for age = 0.747 nmol/L). It is noteworthy that the clonidine test was conducted during the period of undertreated obstructive sleep apnea, reinforcing that this test is more reliable when interfering conditions are removed. Therefore, this patient had primary aldosteronism diagnosis and a false-positive biochemical test for pheochromocytoma caused by a severe obstructive sleep apnea. After surgery, aldosterone decreased to <3 ng/dL and blood pressure became well-controlled with only amlodipine and carvedilol.

Case 2

Plasma metanephrines were repeated to make sure the patient was recumbent for 30 minutes before sampling, and plasma normetanephrine levels remained elevated (1.3 nmol/L; 97.5th percentile for age = 0.6889 nmol/L). Then, we decided to change zolpidem by clonazepam 0.25 mg for 2 weeks and repeat biochemical investigation for PPGL. After zolpidem suspension, plasma normetanephrine normalized (0.5 nmol/L; 97.5th percentile for age = 0.6889 nmol/L) and pheochromocytoma was excluded. Although zolpidem (a $GABA_A$ receptor agonist) is not listed as an interfering medication, we have described here a false-positive biochemical screening caused by zolpidem.

Case 3

The patient underwent laparoscopic right adrenalectomy. She presented hypertensive crisis during the intraoperative period managed with intravenous sodium nitroprusside. Histopathological analysis revealed a pheochromocytoma (PASS score = 3, Ki 67% 2%, chromogranin positive, synaptophysin positive). We present here an adrenal incidentaloma with a false-negative biochemical investigation for pheochromocytoma. Although the patient had a previous surgery without intraoperative complications and negative biochemical investigation, she had an adrenal tumor with >30 HU, a high arterial phase peak enhancement (122 HU), and an absolute washout of 75%, which can happen in pheochromocytomas due to their hypervascularization. False-negative results of plasma normetanephrine and metanephrine measurements might be caused by low metabolization of catecholamines within tumor because of the deficiency in catechol-O-methyltransferase expression.

Conclusions

This expert endocrine consult critically examined the diagnostic intricacies of PPGLs, emphasizing the pivotal role of comprehensive evaluation in accurately identifying these tumors. Our clinical cases underscored the necessity of a meticulous approach that integrates clinical assessment, biochemical testing, and imaging. The potential for false-positive results, especially in the context of adrenergic symptoms, elevated catecholamines, or incidental adrenal tumors, indicated the importance of a cautious and comprehensive approach to correctly diagnosis PPGLs.

Notably, the diagnostic journey is complicated by the varied clinical manifestations of PPGLs, from classic adrenergic paroxysms to atypical presentations in dopamine-secreting or nonfunctional tumors. A careful consideration of patient's medication history, comorbid conditions, and lifestyle factors that can influence biochemical test outcomes is crucial. Additionally, it draws attention to the importance of selecting appropriate diagnostic tests and interpreting their results within the broader clinical context.

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Disclosures

M.Q.A. is an associate editor of the *Journal of the Endocrine Society*. G.F.C.F. has nothing to declare.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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