INTEGRATED MULTI-BIOMARKER PANEL FOR PHEOCHROMOCYTOMA DIAGNOSIS: FRACTIONATED METANEPHRINS, VANILLYLMANDYLIC ACID, CLINICAL CASE

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Abstract

Pheochromocytoma is a rare neuroendocrine tumour that is produced in the adrenal medulla or the inner portion of the adrenal gland. This tumour is characterised by an overproduction of catecholamines, especially adrenaline and norepinephrine, which are chemicals that control the body's stress responses. An excess of these hormones causes hyperfunction of the cardiovascular system and the nervous system and symptoms such as arrhythmia, sustained or paroxysmal hypertension, anxiety, intense cephalalgia, diaphoresis, normal urination, and impulsive weight loss. Due to the hormonal activity of pheochromocytoma, it can impact different organ systems and can be life-threatening if not detected or treated. For diagnostics, a complete multi-biomarker panel was applied, which includes the parameters of fractionated metanephrines (metanephrine and normetanephrine) in 24-hour urine, as well as vanillylmandelic acid (VMA). The results of these biochemical biomarkers estimate the diagnosis, with high sensitivity and specificity.

Keywords: *Pheochromocytoma, metanephrine, normetanephrine, vanylmandelic acid (VMA), urinary biomarkers, neuroendocrine tumour.*

Përmbledhje

Feokromocitoma është tumor i rrallë neuroendokrin, që lind nga qelizat kromafine të medullës së gjendrës mbiveshkore ose të ganglioneve simpatike ekstra adrenale (paraganglioma). Karakterizohet nga sekretimi i tepruar i

katekolaminave si epinefrinë, norepinefrinë dhe dopaminë dhe të metabolitëve të tyre. Diagnostikimi i hershëm është esencial, pasi tumoret e patrajtuar paraqesin rrezik jetik.Rasti klinik paraqet rastin e një pacienti 53-vjeçar me simptoma klasike të feokromocitomës. Për diagnostikim u aplikua paneli i plotë multi biomarkerësh, që përfshin parametrat e metanefrinave të fraksionuara (metanefrina dhe normetanefrina) në urinë 24-orëshe, si dhe acidi vanilmandelik (VMA). Rezultatet e këtyre biomarkerëve biokimikë konfirmojnë diagnozën, me sensitivitet dhe specificitet të lartë.

Fjalë kyçe:*Feokromocitomë, metanefrina, normetanefrina, acidi vanilmandelik (vma), biomarkerët urinare, tumor neuroendokrin.*

Introduction

Surrenal glands

Adrenal glands are paired organs present at the top of each kidney that play an important role in maintaining water balance, Na^+ in the body, controlling blood pressure, and regulating the body's response to stress mechanisms (Eisenhofer, 2023; Morton et al., 2019). Each surrenal or adrenal gland consists of two distinct areas that differ in structure and function**:** the renal cortex (Kierszenbaum et al., 2020) and the adrenal medullus (Mescher, 2021). The adrenal medulla contains chromaffin cells (Kibble, 2020).

Two different types of chromaffin cells are present: 80% of cells produce epinephrine, and 20% of them synthesize norepinephrine (Fassnacht et al., 2023; Shah, 2021). Catecholamines are hormones and neurotransmitters that play a crucial role in the body’s response to stress and sympathetic nervous system activation. Their synthesis begins with the amino acid tyrosine, which is transformed into 3,4-dihydroxyphenylalanine through the action of the tyrosine hydroxylase enzyme. and then will be converted into dopamine by the enzyme 3,4-dihydroxyphenylalanine decarboxylase.

After its formation, dopamine is transported into storage granules within chromaffin cells, where it undergoes further conversion into norepinephrine through the activity of dopamine hydroxylase. In certain cells, norepinephrine can also be converted into epinephrine (Holt et al., 2021). Once catecholamines have exerted their physiological effects, they are metabolised by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

More stable metabolites are created by the breakdown process, including metanephrines and vanillylmandelic acid (VMA), which are subsequently removed in the urine. Urinary measurements of VMA and metanephrines are frequently used in clinical practice to assess excessive catecholamine secretion, especially in patients suspected of having pheochromocytoma or other catecholamine-secreting tumours because these metabolites measure the body's total production of catecholamines (Holt et al., 2021). Pheochromocytoma is a neuroendocrine tumour that develops in the adrenal medulla, the inner part of the adrenal gland (Igaz, 2021). This tumour is characterised by the overproduction of catecholamines, particularly epinephrine and norepinephrine, which are hormones responsible for regulating the body's stress response (Pietroluongo, 2025). Excessive secretion of these hormones leads to overstimulation of the cardiovascular and nervous systems, resulting in symptoms such as rapid heartbeat, persistent or episodic hypertension, anxiety, intense headaches, profuse sweating, and unintended weight loss. Because of its hormonal activity, pheochromocytoma can significantly affect multiple organ systems and may become life-threatening if left undiagnosed or untreated. Most pheochromocytomas are benign and are treated with surgical removal (Khalil, 2025; Bauer, 2024).

Case presentation

A 53-year-old woman was referred for further evaluation of persistent arterial hypertension of unknown origin. Despite treatment with antihypertensive medications, blood pressure remained poorly controlled and reached values of 210/110 mmHg during symptomatic episodes. The patient reported recurrent episodes of severe headache, palpitations, and excessive sweating. These episodes were associated with transient hypertensive crises, whereas blood pressure returned to normal levels between attacks, suggesting intermittent catecholamine secretion.

Table 1. Patient demographics

Age	53 years old
Gender	Female

The patient belongs to the female gender and is 53 years old. After consultation with the endocrinologist, the patient was suggested to have catecholamine tests performed.

Method

A twenty-four-hour urine sample was collected under standardized conditions for the measurement of metanephrine, normetanephrine, and vanillylmandelic acid (VMA). Prior to collection, the patient was instructed to avoid catecholamine-rich foods, caffeine-containing beverages, alcohol consumption, smoking, excessive physical activity, and emotional stress. The urine sample was collected in preservative-containing containers, stored under refrigerated conditions throughout the collection period, and subsequently analyzed according to the laboratory's validated analytical protocols. The patient did not receive alpha/beta-blockers during this period.

Given the suspicion of secondary hypertension, biochemical investigations were performed with the high-performance liquid chromatography method.

Results

Plasma metanephrine concentration was 262.2 μg/dL (reference value <90 μg/dL), plasma normetanephrine concentration was 1900 μg/dL (reference value <650 μg/dL), and urinary vanillylmandelic acid concentration was 10.3 mg/dL (reference value <8 mg/dL). The marked elevation of all three biomarkers strongly suggested a catecholamine-secreting neoplasm.

Table 2. Results of the 24-hour urine biochemical panel

Biomarker	**Patient Value**	**Reference Values**	**Interpretation**
Metanephrine (24h urine)	262.2 μg/dL	30-180 μg/dL	High ↑↑↑
Normetanephrine (24h urine)	1900 μg/dL	128-484 μg/dL	High ↑↑↑
Vanilmandelik Acids (VMA)	10.3mg/dL	1.6-7.3 mg/dL	High ↑

Subsequent radiological imaging identified a well-defined mass measuring 3.6 x 4.2 x 5.1 cm in the left adrenal gland. The combination of resistant hypertension, the classical symptom triad of headache, palpitations, and diaphoresis, markedly elevated catecholamine metabolites, and imaging evidence of an adrenal mass strongly supported the diagnosis of pheochromocytoma.

The patient underwent left adrenalectomy following appropriate preoperative preparation. Histopathological examination of the surgical specimen confirmed the diagnosis of pheochromocytoma. The postoperative course was uneventful, with complete resolution of headache, palpitations, and diaphoresis. Blood pressure normalized, and no further hypertensive episodes were observed during follow-up.

Discussion

In the present case, the patient exhibited the classic clinical presentation of pheochromocytoma, characterized by recurrent headache, palpitations, diaphoresis, and episodes of paroxysmal hypertension. Although this symptom constellation is highly suggestive of catecholamine-producing tumors, pheochromocytoma continues to be regarded as a diagnostic challenge because symptoms are often intermittent and nonspecific.

As a result, many patients experience a significant delay between symptom onset and definitive diagnosis. Early recognition of these characteristic manifestations is essential, given the potentially serious cardiovascular consequences of prolonged catecholamine excess. (Saavedra, 2024), (Gupta, 2024), (Bačun, 2024). Current evidence identifies plasma-free metanephrines and normetanephrines as the most sensitive biochemical markers for the diagnosis of pheochromocytoma.

In the present case, markedly elevated urinary concentrations of metanephrine, normetanephrine, and vanillylmandelic acid (VMA) provided strong biochemical evidence of catecholamine hypersecretion. The substantially higher normetanephrine level compared with metanephrine suggested predominant norepinephrine secretion, a characteristic biochemical profile frequently observed in adrenal pheochromocytomas (Eisenhofer, 2023), Rufolo, 2026).

According to international guidelines from the Endocrine Society, measurement of fractionated plasma free metanephrines or urinary

fractionated metanephrines is recommended as the first-line biochemical test for pheochromocytoma and paraganglioma, with reported sensitivity and specificity reaching approximately 97% and 98%, respectively (Lenders, 2014). The increase in metanephrine is usually more related to the production of adrenaline, while the increase in normetanephrine is associated with the production of norepinephrine. The biochemical findings were consistent with a predominantly noradrenergic (norepinephrine-producing) pheochromocytoma, as evidenced by the disproportionate elevation of normetanephrine relative to metanephrine (Giacché, 2024).

Results should always be interpreted in a clinical context because certain medications, stress, caffeine, tobacco, and other diseases can affect their levels. VMA represents the final product of catecholamine metabolism (via MAO and COMT). Although historically it has been the primary biomarker, the sensitivity of the VMA (62%) is inferior to metanephrines. However, the VMA continues to have value as a confirmatory test. The combination of fractionated metanephrines with VMA: This combination reduces false-negative results due to its high sensitivity and provides information on the biochemical phenotype of the tumor, specifically whether epinephrine or norepinephrine is dominant (Saavedra, 2024; Lenders, 2024; Giacché, 2024).

Conclusion

Pheochromocytoma should be considered in patients presenting with resistant or paroxysmal hypertension, particularly when accompanied by headache, palpitations, and excessive sweating. This clinical biochemical case report demonstrates the effectiveness of the integrated multi-biomarker panel in the diagnosis of pheochromocytoma. Urinary fractionated metanephrines (metanephrine and normetanephrine) are superior biomarkers with high sensitivity, while vanillylmandelic acid remains a useful component of the complete panel.

Early biochemical diagnosis, followed by imaging confirmation and well-prepared surgical treatment, has been established as the first standard in the management of pheochromocytoma.

Histopathological confirmation remains the diagnostic gold standard. Early surgical treatment can result in complete symptom resolution and normalization of blood pressure, thereby preventing potentially life-threatening cardiovascular complications.

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