

SPECIFIC FEATURES OF PHEOCHROMOCYTOMA

Nargis Qodirovna Xasanova

Department of Fundamental Medical Sciences of the Asian International University. Bukhara, Uzbekistan

Annotation: Pheochromocytomas and paragangliomas are catecholamine-producing tumors derived from the sympathetic or parasympathetic nervous system. These tumors may arise sporadically or be inherited as features of multiple endocrine neoplasia type 2 or several other pheochromocytoma-associated syndromes. The diagnosis of pheochromocytomas provides a potentially correctable cause of hypertension, and their removal can prevent hypertensive crises that can be lethal. The clinical presentation is variable, ranging from an adrenal incidentaloma to a patient in hypertensive crisis with associated cerebrovascular or cardiac complications.

Keywords: hypertension, palpitation, headache, epinephrine, tumor.

Pheochromocytoma is a rare, usually benign tumor that develops in the adrenal glands, specifically in the adrenal medulla, where it affects the production of hormones like adrenaline (epinephrine) and noradrenaline (norepinephrine). These hormones regulate the body's fight-or-flight response, which includes increasing heart rate and blood pressure.

EPIDEMIOLOGY:

Pheochromocytoma is estimated to occur in 2–8 of 1 million persons per year, and about 0.1% of hypertensive patients harbor a pheochromocytoma. Autopsy series reveal a prevalence of 0.2%. The mean age at diagnosis is about 40 years, although the tumors can occur from early childhood until late in life. The “rule of tens” for pheochromocytomas states that about 10% are bilateral, 10% are extra-adrenal, and 10% are malignant. However, these percentages are higher in the inherited syndromes.

ETIOLOGY AND PATHOGENESIS

Pheochromocytomas and paragangliomas are wellvascularized tumors that arise from cells derived from the sympathetic (e.g., adrenal medulla) or parasympathetic (e.g., carotid body, glomus vagale) paraganglia (Fig. 6-1). The name pheochromocytoma reflects the black-colored staining caused by chromaffin oxidation of catecholamines. Although a variety of terms have been used to describe these tumors, most clinicians use the term pheochromocytoma to describe symptomatic catecholamine-producing tumors, including those in extraadrenal retroperitoneal, pelvic, and thoracic sites. The term paraganglioma is used to describe catecholamine-producing tumors in the head and neck. These tumors may secrete little or no catecholamines.

The etiology of sporadic pheochromocytomas and paragangliomas is unknown. However, about 25% of patients have an inherited condition, including germ-line mutations in the RET, VHL, NF1, SDHB, SDHC, SDHD, or SDHAF2 genes. Biallelic gene inactivation has been demonstrated for the VHL, NF1, and SDH genes, whereas RET mutations activate the receptor tyrosine kinase activity. SDH is an enzyme of the Krebs cycle and the mitochondrial respiratory chain. The VHL protein is a component of a ubiquitin E3

ligase. VHL mutations reduce protein degradation, resulting in upregulation of components involved in cell cycle progression, glucose metabolism, and oxygen sensing.

CLINICAL PICTURE:

The clinical picture of pheochromocytoma can vary widely, but the most common symptoms are related to the overproduction of catecholamines (adrenaline and noradrenaline) by the adrenal tumor. These symptoms often occur in episodes or "paroxysms" and can be triggered by stress, physical exertion, medications, or even certain foods. Below is a breakdown of the clinical presentation:

1. Cardiovascular Symptoms:

- Hypertension: Persistent or paroxysmal (sudden and severe) high blood pressure, which can be resistant to conventional treatment.
- Tachycardia: Increased heart rate or palpitations.
- Orthostatic hypotension: A drop in blood pressure when standing, leading to dizziness or fainting.
- Chest pain or angina: Due to the strain on the heart.
- Arrhythmias: Irregular heartbeat.

2. Neurological Symptoms:

- Severe headaches: These are often sudden, throbbing, and can be associated with the hypertensive episodes.
- Anxiety or panic attacks: Catecholamine surges can mimic anxiety disorders or panic attacks.
- Tremors: Shaking, particularly of the hands.
- Sweating: Excessive, drenching sweating even without physical activity.
- Blurred vision: Sometimes due to hypertensive episodes.

3. Gastrointestinal Symptoms:

- Nausea and vomiting: May occur due to the high levels of circulating catecholamines.
- Abdominal pain: Can occur but is less common.
- Constipation: Catecholamine excess can slow down the digestive tract.

4. Metabolic Symptoms:

- Weight loss: Due to increased metabolic rate from high catecholamine levels.
- Heat intolerance: Feeling overheated, even in normal conditions.

5. Other Common Symptoms:

- Pallor or flushing: Skin can turn pale or red during episodes.
- Hyperglycemia: High blood sugar due to the effect of catecholamines on glucose metabolism.

PAROXYSMS (Sudden Attacks):

These attacks typically last 15 to 60 minutes and may include a sudden onset of:

- Severe headache
- Sweating

- Palpitations
- A sense of impending doom
- Tremors
- Abdominal pain
- Flushing or pallor

The attacks may be spontaneous or triggered by physical activity, emotional stress, certain medications, or consumption of foods high in tyramine (e.g., aged cheese, red wine).

DIAGNOSIS:

The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging. Both are of equal importance, although measurement of catecholamines is traditionally the first step.

1. Clinical Presentation

- Symptoms: The classic triad includes episodic headache, sweating, and palpitations. Other symptoms may include anxiety, tremors, hypertension (often paroxysmal but can be sustained), weight loss, and hyperglycemia.
- Family History: Since pheochromocytomas may be hereditary (in syndromes like Multiple Endocrine Neoplasia type 2, Von Hippel-Lindau disease, and Neurofibromatosis type 1), family history is important.

2. Biochemical Testing

The first step in diagnosis is to confirm excess catecholamine production through biochemical testing:

- Plasma Free Metanephrines: These are metabolites of catecholamines. Elevated levels in plasma are a key diagnostic marker for pheochromocytoma.
- 24-Hour Urinary Fractionated Metanephrines and Catecholamines: Another highly sensitive test that measures catecholamines and their metabolites over a 24-hour period.
- Plasma Catecholamines: This test may be less sensitive but can be useful in some cases.

3. Imaging Studies

Once biochemical confirmation is achieved, imaging is performed to localize the tumor:

- CT Scan (Computed Tomography): This is often the first imaging test to locate the adrenal tumor.
- MRI (Magnetic Resonance Imaging): MRI is preferred in certain cases, especially for extra-adrenal pheochromocytomas or for patients who cannot undergo CT scans (e.g., due to radiation concerns).
- MIBG Scan (Metaiodobenzylguanidine): This nuclear medicine scan is used if CT/MRI does not clearly localize the tumor or if multiple tumors are suspected. MIBG specifically binds to catecholamine-producing tissues.
- PET Scan: Sometimes used in difficult-to-localize or metastatic pheochromocytoma.

4. Genetic Testing

If there is a family history of pheochromocytoma or the patient is diagnosed at a young age, genetic testing may be recommended to evaluate for hereditary syndromes such as MEN2, VHL, or others.

5. Preoperative Evaluation

Once a pheochromocytoma is confirmed, careful preoperative management is necessary to prevent hypertensive crises during surgery:

- Alpha-Blockers (e.g., phenoxybenzamine or doxazosin) are used to control blood pressure and reduce the risk of intraoperative complications.
- Beta-Blockers: Only used after adequate alpha-blockade, as giving beta-blockers first can worsen hypertension.

6. Definitive Diagnosis (Histopathology)

- Surgical Removal: The definitive diagnosis of pheochromocytoma is made by histopathological examination of the excised tumor after surgery. Laparoscopic adrenalectomy is the usual treatment for localized tumors.

CONCLUSION: Pheochromocytoma is a rare tumor of the adrenal medulla composed of chromaffin cells and is part of the paraganglioma (PGL) family of tumors, being defined as an intra-adrenal PGL.

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