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Educational Case: Pheochromocytoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, endocrine, pheochromocytoma, paraganglioma, adrenal tumor, multiple endocrine neoplasia, secondary hypertension, familial pheochromocytoma-paraganglioma syndrome

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Primary Objective

EN5.3: Pheochromocytoma and Paraganglioma: Outline the clinicopathologic features of pheochromocytoma and compare and contrast the hereditary cancer syndromes associated with paragangliomas/pheochromocytomas.

Competency 2: Organ System Pathology; Topic EN: Endocrine. Learning Goal 5: Endocrine Neoplasms.

Part 1: Clinical Case

Patient Presentation

A 47-year-old male with no previous medical history presents to his family physician complaining of episodic headaches, sweating, heart palpitations, and a tremor. The symptoms started a few years ago, have become more frequent, and can last anywhere between a few seconds to an hour. The episodes often occur when the patient feels stressed or exercises. He is frustrated because nothing he does changes the severity of his symptoms. He does not have a history of serious illnesses, hospitalizations, or trauma. He is not on any medications. He has a family history of hypertension. He does not use tobacco products, cocaine, methamphetamines, or any other illicit drugs. He has not had fevers, chills, chest pain, shortness of breath, nausea, vomiting, or diarrhea.

On physical examination, vital signs showed an elevated blood pressure of 168/96 mm Hg, tachycardia of 116 beats per minute, a respiratory rate of 20 breaths per minute, and a temperature of 98°F (36.66°C). Physical examination reveals a diaphoretic male with no cardiopulmonary abnormalities other than the previously mentioned tachycardia.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis Based on the History and Physical Examination?

The differential diagnoses of episodic headaches, sweating, heart palpitations, and a tremor include pheochromocytoma, paraganglioma, essential hypertension, anxiety disorders, panic attack, thyrotoxicosis, medications, amphetamine and cocaine abuse, paroxysmal supraventricular tachycardia, and carcinoid syndrome. Neuroendocrine tumors secreting insulin (insulinoma)

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Table 1. Signs and Symptoms of a Pheochromocytoma.[1]

1. Sustained or paroxysmal hypertension
2. Tachycardia
3. Palpitations
4. Headache
5. Sweating
6. Tremor
7. A sense of apprehension

and heart failure are other considerations. A good medical history and imaging studies excludes several of these entities.

Part 2: Diagnostic Findings

Laboratory Studies

The complete blood count, comprehensive metabolic panel, D-dimer, and serial troponins were within reference ranges. An electrocardiogram indicated sinus tachycardia and left axis deviation consistent with left ventricular hypertrophy. A 24-hour urine fractionated metanephrine and catecholamine test showed significant elevations. Urinary metanephrines were 1300 μg/24 hours (normal range: 45-290 μg/24 hours).

Imaging

A chest X-ray was performed demonstrating mild left ventricular hypertrophy. Cardiac ultrasound demonstrated ventricular hypertrophy. No other abnormalities were present. An abdominal computed tomography (CT) scan showed a 3-cm-diameter left adrenal gland mass. The right adrenal gland was unremarkable.

Questions/Discussion Points, Part 2

What Entities Are in the Differential Diagnosis Based on the Above Laboratory Findings?

Elevated metanephrines and catecholamines are characteristic of a pheochromocytoma or paraganglioma.[1] Anxiety and panic disorders are also in the differential. Medications, for example, tricyclic antidepressants, are another consideration. Metanephrines may also be elevated in neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Measurement of urinary homovanillic acid and vanillylmandelic acid is the preferred screening laboratory test for these 3 entities.

Based on the Imaging Findings, What Entities Are in the Differential Diagnosis of an Adrenal Mass?

Pheochromocytoma, especially with elevated metanephrines, is the main consideration. Adrenal adenoma, adrenal carcinoma, myelolipoma, cyst, lipoma, metastatic cancer, hyperplasia, or tuberculosis can present as an adrenal mass.[2] Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma also present as adrenal masses. Paraganglioma would be an extra-adrenal mass.

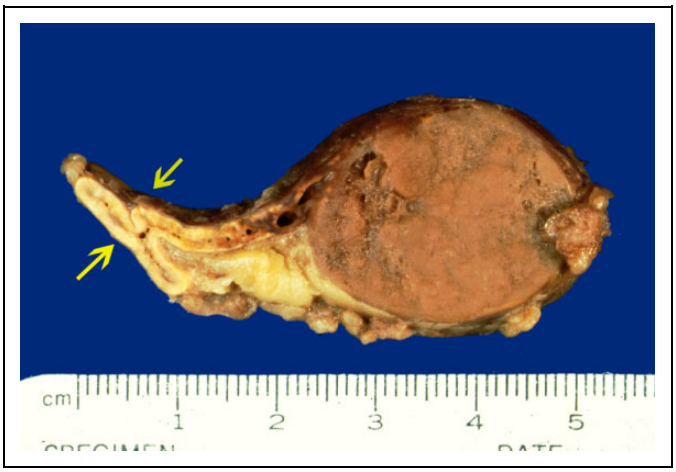

Figure 1. The adrenal gland is replaced with a central 3-cm-diameter brown tumor. A small portion of residual adrenal gland is present (arrows).

What Is the Diagnosis Based on the Clinical Scenario?

The paroxysmal headaches, sweating, heart palpitations, and hypertension (Table 1) with an abnormal 24-hour urine fractionated metanephrine and catecholamine test are consistent with a pheochromocytoma. This diagnosis is supported by an adrenal mass. The triad of headache, sweating, and heart palpitations should raise suspicion of a pheochromocytoma, especially when concurrent hypertension exists, but the triad is seen in less than 25% of patients with pheochromocytomas.[1-4]

Part 3: Diagnostic Findings

What Would Be the Next Step to Confirm the Diagnosis?

An adrenalectomy is indicated. Examination of the surgically removed adrenal gland showed a central brown tumor mass that originated in the adrenal medulla (Figure 1). Microscopic examination showed cells with abundant granular cytoplasm arranged in small nests surrounded by a thin fibrovascular stroma (Figure 2). Immunohistochemistry for the neuroendocrine markers, chromogranin and synaptophysin in the chief cells and S100 in the sustentacular cells were positive, supporting the diagnosis of a pheochromocytoma.

Questions/Discussion Points, Part 3

The gross and histological appearance of the tumor confirms the diagnosis. The term "pheochromocytoma" comes from the "dusky color" (dark brown) the tumor develops when immersed in a potassium dichromate solution.[1,4] Pheochromocytomas vary in appearance from well-circumscribed lesions to large hemorrhagic masses weighing up to 4 kg. On average, most pheochromocytomas weigh approximately 100 g.[1,2,4]

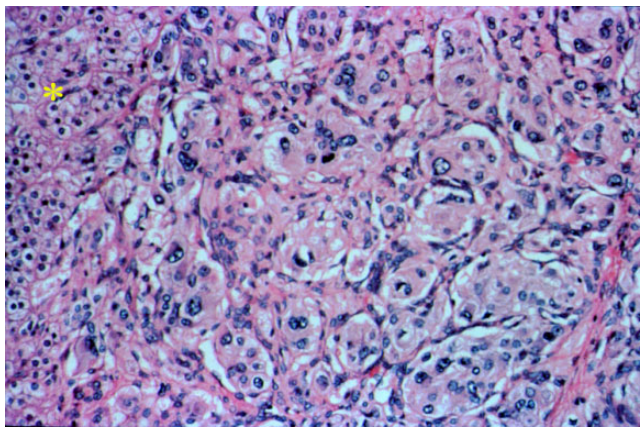

Figure 2. Polyhedral tumor cells with eosinophilic granular cytoplasm and ovoid nuclei are arranged in a characteristic alveolar "zellballen" or nesting pattern surrounded by thin fibrovascular septa. Residual adrenal cortex is present at the periphery (*). H&E, intermediate magnification.

Histology is variable in pheochromocytomas. The nesting, alveolar (zellballen) pattern is one of the more common patterns observed in pheochromocytomas. Polygonal to spindle-shaped chief cells surrounded by sustentacular cells give rise to the nesting pattern (Figure 2). Round to oval nuclei with a stippled chromatin pattern, commonly referred to as a salt and pepper pattern, is characteristic of neuroendocrine tumors including pheochromocytomas. Other histologic patterns observed on light microscopy include a diffuse, spindle, or small cell pattern, or a trabecular arrangement or sclerotic pattern. Immunohistochemistry and electron microscopy demonstrating membrane-bound secretory granules are helpful when the histologic pattern is equivocal.[1-4]

Malignant behavior absent metastatic disease is difficult to predict.[1-3] Pheochromocytomas with bland histology have metastasized to lymph nodes, liver, and lung.[2] In contrast, pheochromocytomas with marked pleomorphism have not been associated with metastases. As a generality, larger tumors with significant necrosis have a greater chance of being malignant. Histology in combination with the following factors (cellularity, necrosis, capsular or vascular invasion, type of catecholamine secreted, and MIB-1 immunoreactivity) is proposed to classify tumors from well differentiated to poorly differentiated with a 10-year survival based on degree of differentiation.[2]

What Is a Pheochromocytoma? How Does It Differ From a Paraganglioma?

Pheochromocytomas and paragangliomas are uncommon neuroendocrine tumors. A pheochromocytoma is a catecholamine-secreting tumor that develops from chromaffin cells in the adrenal medulla. The annual incidence is between 0.4 and 9.5 per 100 000 population. More recent data indicate that 1.5% to 18% of adrenal incidentalomas discovered during abdominal imaging for various reasons represent pheochromocytomas.[4,5] Most pheochromocytomas are sporadic and solitary tumors. Bilateral tumors are frequently observed in familial (hereditary) syndromes. Sporadic pheochromocytomas predominantly occur in adults, with the highest number in patients between 40 and 50 years of age.[4] Ten percent occur in children. Tumors associated with familial syndromes occur at an earlier age. The male:female ratio is equal.[4] Pheochromocytomas secrete both norepinephrine and epinephrine and present with the clinical findings in Table 1. Complications are listed in Table 2. Malignant potential is addressed above.[1-3]

Table 2. Possible Complications of a Pheochromocytoma.[1]

1. Catecholamine cardiomyopathy
2. Congestive heart failure
3. Pulmonary edema
4. Myocardial infarction
5. Ventricular fibrillation
6. Cerebrovascular accidents

The autonomic nervous system is divided into parasympathetic and sympathetic branches. Aggregates of autonomic neuronal cell bodies, referred to as ganglia, represent the cell bodies of postsynaptic neurons. Chromaffin cell tumors that have an extra-adrenal location arising from the sympathetic and parasympathetic ganglia (paraganglia) are called paragangliomas. Parasympathetic ganglia are mainly localized in the head and neck region. The carotid body tumor is an example of a parasympathetic paraganglioma. It is more frequent at high altitudes. Other sites include the vagus nerve, middle ear, and larynx.[2,3,6] Sympathetic ganglia are located along the vertebral bodies in the abdomen, pelvis, and thorax and sympathetic chain. Sites of involvement for sympathetic paragangliomas include the aortic bifurcation (Organ of Zuckerkandl), urinary bladder, heart, gallbladder, uterus, and adjacent to the spinal cord.[2,3,6] Paragangliomas possess the potential to secrete the catecholamine norepinephrine. Most paragangliomas in the head and neck region are nonfunctional with symptoms based on location. Malignant potential is approximately 5% for carotid body tumors and treatment is surgical resection. Germline mutations, as part of the hereditary paraganglioma syndrome, involving the succinate dehydrogenase gene, are observed.[2,3,6,7]

What Are the Possible Complications of a Pheochromocytoma?

Complications are often due to the sudden release of catecholamines (Table 2). Sudden release can cause congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, and cerebrovascular accidents. It can also lead to catecholamine cardiomyopathy.[1] Malignant behavior with metastases is another complication.

Table 3. Hereditary Cancers Associated With Pheochromocytoma and Paragangliomas.[1-4,6,7]

Gene	Chromosome	Syndrome	Associated Features
RET	10q11.21	Multiple endocrine neoplasia 2A	Pheochromocytoma Medullary thyroid carcinoma Parathyroid hyperplasia
RET	10q11.21	Multiple endocrine neoplasia 2B	Pheochromocytoma Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous ganglioneuromas
NF1	17q11.2	Neurofibromatosis, type 1	Pheochromocytoma Neurofibromatosis Café-au-lait spots Optic nerve glioma
VHL	3p25.3	Von Hippel-Lindau	Pheochromocytoma, paraganglioma
SDHA	5p15.33	Familial paraganglioma type 5	Pheochromocytoma, paraganglioma
SDHB	1p36.13	Familial paraganglioma type 4	Pheochromocytoma, paraganglioma
SDHC	1q23.3	Familial paraganglioma type 3	Pheochromocytoma, paraganglioma
SDHD	11q23.1	Familial paraganglioma type 1	Pheochromocytoma, paraganglioma
SDHAF2	11q12.2	Familial paraganglioma type 2	Pheochromocytoma, paraganglioma

What Different Hereditary Syndromes Are Associated With Pheochromocytoma and Paragangliomas?

Thirty percent of pheochromocytomas are familial with autosomal dominant inheritance and are associated with genetic mutations (Table 3).[1,7] Hereditary pheochromocytomas and paragangliomas occur in younger individuals, 15 to 20 years younger than those with sporadic tumors.[6] The mean age for pheochromocytomas in these individuals is 26 years (range: 12-48 years) and 29 years (range: 5-59 years) for paragangliomas.[3,4,6] Genetic mutations are classified into 2 groups, mutations involving the kinase signaling pathway (*RET* and *NF1*) and those with increased activity of the hypoxia-induced factor 1 (HIF-1α) transcription factor (*VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*).[1,7]

Von Hippel-Lindau syndrome is associated with a mutation in the *VHL* tumor suppressor gene. Clinically, Von Hippel-Lindau syndrome is characterized by headache, dizziness, weakness, visual deficits, and hypertension with a disease frequency of 1 in 30 000 to 40 000.[3] Symptoms are related to the underlying pheochromocytoma and hemangioblastomas in the brain and spinal cord and angiomas involving the retina and genitourinary tract. Cysts are frequent in the kidney and pancreas. There is also an increased incidence of renal cell carcinoma and neuroendocrine tumors. The *VHL* gene encodes for a protein downregulating HIF-1α leading to overexpression of vascular endothelial growth and other growth factors.[3,7]

Multiple endocrine neoplasia type 2 (MEN 2) syndrome with a prevalence of 1/40 000 individuals is associated with a mutation in the *RET* proto-oncogene that encodes for a receptor tyrosine kinase for glial-derived neurotropic factor. RET is present in urogenital and neural crest precursor cells as well as in the sympathetic, parasympathetic, and enteric nervous system. Multiple intracellular pathways involved in cell growth and differentiation are activated due to *RET* germline mutations.[7] Clinical features related to the underlying neoplasms include thyroid nodules and adenopathy secondary to medullary carcinoma and diarrhea secondary to high calcitonin levels. Symptoms secondary to parathyroid-related hypercalcemia or catecholamine release from a pheochromocytoma are less common.

Neurofibromatosis type 1 syndrome has an approximate frequency of 1 in 3000 and is associated with a *NF1* gene mutation that codes for the protein neurofibromin.[3,7] Neurofibromin acts as a negative regulator of RAS signaling. Loss of neurofibromin function leads to excessive RAS signaling. Clinical features include café au lait skin lesions, cutaneous and visceral neurofibromas, Lisch nodules, optic gliomas, and osseous lesions. Malignant nerve sheath tumors are also observed.[3,7]

Succinate dehydrogenase is a mitochondrial enzyme. Structurally, it is composed of 4 subunits: SDHA, SDHB, SDHC, and SDHD. Mutations involving these subunits affecting HIF-1α transcription factor lead to hereditary paraganglioma syndrome, a syndrome characterized by multiple paragangliomas and pheochromocytomas with a frequency of 1/300 000 (Table 3).[3,6,7] Familial paraganglioma variants, types 1, 3, and 4 are associated with mutations in *SDHD, SDHC*, and *SDHB* genes, respectively. Familial paraganglioma type 5 is associated with mutation in *SDHA* and familial paraganglioma type 2 with mutation in *SDHAF2* gene. Clinical features for patients with paragangliomas are based on the presence of a slow growing mass, tumor location (impingement on a critical structure), and whether the tumor is hormonally active. In contrast to pheochromocytomas that are frequently hormonally active, paragangliomas are less hormonally active. Many patients are asymptomatic with the lesion discovered during imaging workup for an abdominal condition or at autopsy.[4]

Each of the above hereditary syndromes, involving mutations in the succinate dehydrogenase gene, must be considered when evaluating a patient with a pheochromocytoma and/or paraganglioma.[1-4,6-12] Patients presenting at an early age with these neoplasms should be screened for mutations involving the succinate dehydrogenase gene.

Immunohistochemistry for SDHB has been used to screen for succinate dehydrogenase mutations.[2]

What Is the Rule of 10s?

Historically, the rule of 10s was applied to pheochromocytomas. The 10% rule outlined that 10% of pheochromocytomas (paragangliomas) were extra-adrenal, 10% of pheochromocytomas were bilateral, 10% were malignant, 10% were not associated with hypertension, and 10% occurred in children.[1] The 10% rule is called into question because tumor location (adrenal vs extra-adrenal) and likelihood of malignancy vary based on genetic mutations. Genetic involvement in tumors is closer to 30%. Fifty percent of familial pheochromocytomas are bilateral. Twenty to forty percent of paragangliomas are malignant and malignancy is more common in chromaffin tumors associated with germline mutations.[1-4,6,7]

Teaching Points

- A pheochromocytoma should be considered when evaluating an adrenal mass.
- The triad of headache, sweating, and heart palpitations should raise suspicion of a pheochromocytoma, especially when concurrent hypertension exists.
- Diagnosis of a pheochromocytoma is based on pathologic findings and is supported by an abnormal 24-hour urine fractionated metanephrine and catecholamine test.
- Pheochromocytomas are catecholamine-secreting tumors that originate in the adrenal medulla.
- Pheochromocytoma complications from catecholamine secretion include congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, cerebrovascular accidents, and catecholamine cardiomyopathy.
- Paragangliomas are catecholamine-secreting tumors that arise from the autonomic nervous system ganglia that represent the cell bodies of postsynaptic neurons. Paragangliomas affect both the sympathetic and parasympathetic chains of the autonomic nervous system.
- Sign and symptoms associated with paragangliomas are based on tumor location, rate of growth, and whether they are hormonally active.
- Thirty percent of pheochromocytomas are familial with autosomal dominant inheritance and are associated with genetic mutations. Genetic mutations are classified into 2 groups, mutations involving the kinase signaling pathway (*RET* and *NF1*) and those with increased activity of the HIF-1α transcription factor (*VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*).
- The diagnosis of a pheochromocytoma at a young age warrants clinical and genetic testing for MEN2 syndrome, Von Hippel-Lindau syndrome, neurofibromatosis 1, and familial paraganglioma–pheochromocytoma syndromes.
- Malignant behavior absent metastatic disease is difficult to predict in these neuroendocrine tumors. Histology in combination with the following factors (cellularity, necrosis, capsular or vascular invasion, type of catecholamine secreted, and MIB-1 immunoreactivity) is proposed to classify tumors from well differentiated to poorly differentiated.

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