Pheochromocytoma

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Abstract: Pheochromocytomas are tumors arising from the chromaffin cells of the adrenal medulla. They are equivalent to paragangliomas in other anatomic sites. They are uncommon neoplasms and most are sporadic, although 10% are described in syndromes, another 10% are bilateral (usually syndrome associated), and about 10% are malignant. They develop in both genders and peak in the fourth to fifth decades, although familial tumors occur at a younger age. Patients present clinically with the pharmacologic effects of excess catecholamines, manifested by episodic, postural, paroxysmal and/or labile hypertension, headaches, diaphoresis, palpitations, chest pain, and anxiety. Radiographic studies with nucleotide scans are often diagnostic. Malignant pheochromocytomas have historically required the presence of metastatic tumor to confirm the diagnosis of a malignant neoplasm. However, a series of histologic features, when used in conjunction with laboratory findings, radiographic findings, macroscopic features, and immunohistochemical results, can help to prospectively diagnose malignant pheochromocytoma. These features include invasion, large nests or diffuse growth (loss of Zellballen architecture), focal or confluent necrosis, high cellularity, tumor cell spindling, cellular monotony, increased mitotic figures, atypical mitotic figures, profound nuclear pleomorphism, and hyperchromasia. Overall, the patient prognosis for benign pheochromocytoma is excellent, although that for malignant pheochromocytoma is intermediate, with surgery achieving the best clinical result of about 75% 5-year survival. Separation from benign pheochromocytoma and adrenal cortical neoplasms is important as the management is different.

Key Words: adrenal, pheochromocytoma, malignant, immunohistochemistry, prognosis

Case Report

A 48-year-old woman presented to her primary care physician with intermittent episodes of intense diaphoresis associated with nausea and a severe headache, present for a few hours at a time, recurring every 2–3 weeks. She felt it worsened if she changed position rapidly. She also reported a history of diarrhea and epistaxis. Her medical history and family history were noncontributory. Physical examination disclosed severe hypertension (220/130 mm Hg) and a palpable mass in the left lower quadrant. Radiographic studies revealed an 8.8-cm mass in the left suprarenal region, yielding a very bright signal on T2-weighted magnetic resonance imaging (MRI). She was taken to surgery with preoperative medical blockade. The mass showed small fragments of residual adrenal cortical tissue at the periphery, with hemorrhage and necrosis in the center of the mass. The tumor cells invaded through the adrenal gland capsule and were noted within vascular channels. The cells were arranged in diffuse sheets and focally in small alveoli, with areas of central necrosis. The cells were large, with an increased nuclear to cytoplasmic ratio, prominent nucleoli, profound nuclear pleomorphism, and increased mitotic figures, including atypical forms. The neoplastic cells were chromogranin immunoreactive, while wisps of S-100 protein reactive cytoplasm were occasionally observed. A diagnosis of malignant pheochromocytoma was rendered.

Introduction

Pheochromocytoma ("dusky color") is a catecholamine-secreting tumor arising from the chromaffin cells of the sympathoadrenal system. Most of pheochromocytomas arise from the adrenal medulla, where the largest collection of chromaffin cells is found.¹⁻³ These tumors are also referred to as paragangliomas when they arise from sympathetic paraganglia. The majority of pheochromocytomas have a benign clinical course but can have a malignant potential. A 10% rule of thumb can be applied to this tumor: 10% bilateral, 10% extraadrenal, 10% malignant, 10% in childhood, and 10% familial.

Clinical

Pheochromocytomas are rare tumors with an estimated incidence of 8/1,000,000 population. Most pheochromocytomas (90%) are sporadic and about 10% are familial, whether
part of a specific syndrome or arising in a familial setting. Syndromes include MEN2A or 2B, Von Recklinghausen disease, and von Hippel-Lindau disease, among others (Table 1). In general, pheochromocytomas associated with a syndrome tend to behave in a benign fashion. In a sporadic setting, >95% of cases are solitary, unilateral lesions, while the remaining tumors are bilateral. Within familial patients, >50% are bilateral and/or multicentric. The peak age in sporadic cases is in the fifth decade, although there is a wide age range at presentation (infancy up to the ninth decade). Familial cases tend to be diagnosed within the first 2 decades of life. Pediatric patients account for about 10% of tumors, where there is also an increased incidence of bilateral and multicentric disease. In general, there is no gender predilection.

Symptoms are referable to the excess catecholamine production and include episodic, sustained, labile, and/or paroxysmal (erratic) hypertension, frequently induced by postural changes, palpitations, headaches, diaphoresis, flushing, anxiety, weakness, syncope, dizziness, nausea, vomiting, epistaxis, constipation, and pain. The classic diagnostic triad is paroxysmal hypertension, headaches, and diaphoresis. The type of tumor hormone production may be associated with differences in the type of hypertension: norepinephrine is more frequently associated with sustained hypertension, while epinephrine, along with norepinephrine, is associated with episodic hypertension. Pure epinephrine-secreting tumors may be associated with hypotension. Occasionally, a palpable abdominal mass may be the presenting symptom.

Laboratory investigation is vital to the diagnostic workup of pheochromocytoma and includes remarkably elevated levels of serum and/or urine catecholamines, norepinephrine, epinephrine, metanephrine, dopamine, vanillylmandelic acid (VMA), or other metabolites. It has been suggested that dopamine values specifically may correlate more closely with malignant pheochromocytoma.

**Radiologic Features**

Preoperative localization of pheochromocytoma is possible with a combination of techniques, including abdominal x-ray, ultrasonography, high-resolution computed tomography, MRI, and nuclear medicine studies. Benign lesions are characteristically homogeneous, fairly well-circumscribed masses. Cystic degeneration, calcification, hemorrhage, and necrosis lead to a nonhomogeneous appearance, especially on contrast enhanced imaging. On T2-weighted images with MRI, pheochromocytomas typically show high signal intensity and appear bright on imaging, sometime referred to as the “light-bulb” sign (Fig. 1). The use of the radiopharmaceutical and guanethidine analog 131I-meta-iodobenzylguanidine (MIBG) for scintigraphy shows a remarkable affinity for adrenal medullary tissue but does not distinguish between different neuroendocrine tumors types. Angiography reveals a vascular tumor mass in the adrenal gland but is seldom employed any longer. Malignant pheochromocytomas are not reliably separated from benign tumors, but they do tend to be larger, displace the kidney due to a mass effect, and may show internal septations, fluid levels, and areas of necrosis (Fig. 2). Furthermore, radiographic studies may show lytic bone lesions or “hypervascular” masses in the liver, lung, spleen, kidney, pancreas and/or lymph nodes that are presumed to represent metastatic disease.

**Fine-Needle Aspiration Biopsy**

Fine-needle aspiration of pheochromocytoma is generally not recommended as it may result in significant hemorrhage, and manipulation of a functional tumor can produce hypertensive crisis. However, in unsuspected cases, the FNA specimens are usually hypercellular, with cells arranged singly or in small groups, often creating a “pseudorosette.” Cells are of small to moderate size and polygonal, with delicate, granular cytoplasm; spindle cells with ample cytoplasm and elongated nuclei; and large, “straplike” cells with large,

**TABLE 1. Selected Genetic Syndromes Associated with Pheochromocytoma**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Locus</th>
<th>Gene</th>
<th>Paraganglia Tumor</th>
<th>Other Abnormalities</th>
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</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau</td>
<td>3p26</td>
<td>VHL</td>
<td>Pheochromocytoma in 10%–20%</td>
<td>Renal cysts and renal cell carcinoma</td>
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<td></td>
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<td>Visceral organ cysts</td>
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<td></td>
<td></td>
<td>Hemangioblastomas</td>
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<tr>
<td>Neurofibromatosis type 1 (von Recklinghausen disease)</td>
<td>17q11.2</td>
<td>Neuro-fibroma</td>
<td>Pheochromocytoma in 1%–5%</td>
<td>Neurofibromas</td>
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<td>Schwannomas</td>
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<td>CNS gliomas</td>
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<tr>
<td>MEN 2A</td>
<td>10q11.2</td>
<td>RET</td>
<td>Pheochromocytoma in 50%–70%</td>
<td>Parathyroid hyperplasia</td>
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<td>Medullary thyroid carcinoma</td>
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<td>Medullary thyroid carcinoma</td>
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<td>Mucosal neumomas</td>
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<td>Skeletal abnormalities</td>
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<tr>
<td>MEN 2B</td>
<td>10q11.2</td>
<td>RET</td>
<td>Pheochromocytoma in 50%–70%</td>
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</tbody>
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eccentric nuclei with prominent nucleoli. All 3 cell types are interspersed throughout the smear, requiring complete examination of the aspirated material.

Pathologic Features

Macroscopic Findings

Pheochromocytomas are typically well circumscribed and spherical or oval in shape (Fig. 3). The chromaffin reaction can be used to demonstrate catecholamines in the tumor. The tumor is immersed in a dichromate fixative, yielding a deep brown appearance as the catecholamines oxidize. Tumors weigh between 12 and 650 g (mean, 200 g) and measure 1 to 18 cm in greatest size (mean, 6 cm). Larger tumors may suggest malignancy or a worse prognosis, but this finding is not universal. On cut section, the tumors are usually firm with a glistening gray-white surface. Some tumors exhibit degenerative changes such as congestion, hemorrhage, necrosis, and even cystic change. Although they may appear encapsulated, close inspection shows a “pseudo-capsule.” Malignant tumors may obscure the central compartment of the adrenal gland from which they arise. Malignant tumors tend to be nodular, lobulated, or bosselated masses, with a variegated cut surface showing mottled areas of hemorrhage, necrosis, calcification, and cystic degeneration. The tumor can be fixed to the surrounding structures, occasionally infiltrating into the substance of the adrenal cortex and periadrenal adipose tissue (Fig. 4). The adrenal cortex may be atrophic or may show paradoxical hyperplasia in response to the hypertension. The majority of patients present with unilateral disease, with bilateral tumors almost exclusively identified in patients with syndrome association (Fig. 5).

Microscopic Findings

Pheochromocytomas are made up of a dual cell population composed by chief cells or pheochromocytes (chromaffin cell) and a second population of sustentacular cells, which are believed to be “supporting” cells, similar to the glial cells in the central nervous system. A number of different architectural patterns may be present, but often one pattern predominates. “Zellballen” (alveolar or nested; Fig. 6)
and trabecular patterns are seen most commonly. Solid, diffuse, and spindle cell patterns are rare and are not dominant. The balls of cells are supported by a rich vascular plexus and a delicate, dendritic to spindle cell sustentacular meshwork (Fig. 7). The cells are polygonal and may have sharply defined cell borders or may interdigitate with indistinct borders. The cytoplasm of the neoplastic cells varies from eosinophilic to basophilic and typically has a finely granular character (Fig. 8). Nuclei are round to oval in shape with a stippled “salt and pepper” chromatin pattern. The cytoplasm may be vacuolated in some cases and may also display PAS-positive globules (Fig. 9). Pleomorphism may be present and bizarre hyperchromatic nuclei, often with intranuclear cytoplasmic inclusions, are common (Fig. 9). Mitotic activity is sparse, and usually <3/10 HPFs. The second population is that of slender sustentacular supporting cells, which are difficult to identify absolutely on light microscopy. They have thin wisps of cytoplasm encompassing the chief cells and are accurately identifiable only with special studies such as S-100 protein immunohistochemistry.2,3,5,7,19–21 Degenerative changes such as fibrosis, hemorrhage, hemosiderin deposition, and cystic change can also be seen, while stromal amyloid and melanin is occasionally identified (Fig. 10).

The most rigorous definition of malignancy requires that metastases must be present at a site where chromaffin tissue is not otherwise found, thereby excluding the possibility of misclassifying multicentric primary lesions as metastases or the development of locoregional recurrence.3,7,10,11,19,21,22

FIGURE 4. This malignant pheochromocytoma has hemorrhage, necrosis and invasion into the surrounding kidney and liver (courtesy Dr. R. R. de Krijger and Dr. P. Komminoth).

FIGURE 5. An example of bilateral pheochromocytomas identified in a suprarenal location in a patient with familial disease (courtesy Dr. J. Hunt).

FIGURE 6. Small nests of cells (“Zellballen”) are characteristic of pheochromocytoma.
Therefore, the prospective diagnosis of a malignant pheochromocytoma on histologic criteria alone is exceedingly difficult. However, an accumulation of specific histologic criteria has shown promise in the prospective diagnosis of malignant pheochromocytoma. These histologic features are strongly associated with malignant pheochromocytoma, although each individually is not unique or specific for malignant behavior. Therefore, perhaps a weighting of these features may be able to predict a more biologically aggressive behavior (Table 2): (1) capsular invasion; (2) vascular invasion (Fig. 11); (3) extension into the periadrenal adipose tissue (Fig. 12); (4) expanded, large, and confluent nests (a “large nest” is defined as 3 to 4 times the size of a normal size of the medullary paraganglia nests) (Fig. 13); (5) diffuse growth (the rich vascular sustentacular supporting framework is not identifiable); (6) necrosis (apoptosis, central comedonecrosis in the large nests, or confluent) (Fig. 14); (7) increased cellularity; (8) tumor cell spindling (Fig. 12); (9) profound cellular and nuclear pleomorphism; (10) cellular monotony (usually with smaller cells having high nuclear to cytoplasmic ratio); (11) nuclear hyperchromasia; (12) macronucleoli; (13) increased mitotic figures (>3 per 10 high-power fields; and (14) any atypical mitotic figures. A score
of 4 or higher is associated with malignant behavior, while a score of <4 is associated with benign behavior. Let me hasten to add, however, that any scoring scale must only be applied as an adjunct to the clinical information, size and weight, and immunohistochemical studies to achieve the best overall patient outcome.

The histology of the metastatic deposits which can often be identified in the lymph nodes or other organs is generally similar, although occasionally “maturation” of the tumor into a more characteristic Zellballen pattern is seen (Fig. 15).

**Special Studies**

**Ultrastructural Features**

The diagnostic hallmark is dense-core neurosecretory granules that range in size from 150 to 250 nm. Norepinephrine granules are distinguished from epinephrine granules by a large, eccentric, electron-lucent zone or “halo” between the dense core and the granule membrane. Epinephrine granules tend to be more uniform.
Immunohistochemistry

Pheochromocytes characteristically and invariably stain with chromogranin and synaptophysin (Fig. 16). While unnecessary for the diagnosis, pheochromocytes express a broad range of neuroendocrine markers and neuropeptides, including neuron specific enolase, CD56 (membrane), CD99, leu- and met-enkephalins, serotonin, somatostatin, calcitonin, and substance P. The supporting sustentacular cell population at the periphery of the tumor nests is highlighted with antibodies to S-100 protein (Fig. 17). The S-100 protein positive sustentacular cells often show diminished to absent reactivity in both quantity and quality in areas of large nests and diffuse growth, a feature much more commonly seen in malignant pheochromocytoma (Fig. 17). There is no tumor cell immunoreactivity with inhibin.2,3,5,9,20,21

DNA Content

Tetraploid and aneuploid populations are present in both benign and clinically malignant pheochromocytomas,
but while a tetraploid or aneuploid tumor population does not confirm a malignant diagnosis, it may suggest a more aggressive biologic behavior.24,25

**Genetic Studies**

A group of susceptibility genes has been identified and includes the RET proto-oncogene (associated with multiple endocrine neoplasia type II) and the tumor suppressor gene VHL (associated with von Hippel-Lindau disease). Pheochromocytomas and glomus tumors are increased in patients who have germline mutations in several genes which encode the various subunits of the succinate-ubiquinone oxidoreductase gene (SDH), which is an enzyme in the mitochondrial respiratory chain complex II. These genes include PGL1, which encodes SDH subunit D (on 11q23); PGL2 mapping to 11q13; PGL3, which encodes SDH subunit C (on 1q21); and PLG4, which encodes the SDH subunit B (on 1p36). Interestingly, point mutations and/or deletion mutations in these genes can also be identified in up to 20% of patients with presumed spontaneous paragangliomas.2,26–30

**Differential Diagnosis**

Whereas a number of different tumors need to be considered in the differential diagnosis, separation of a benign from a malignant pheochromocytoma is the more difficult distinction. The presence of metastatic disease clinches the diagnosis. However, metastasis is often undocumented at the time of the initial evaluation. While none of the features above makes the diagnosis absolute, the presence of an aggregate of these changes suggests a more aggressive biologic behavior.

An adrenal cortical neoplasm (adenoma or carcinoma) does not have the same architectural pattern. Cortical neoplasms tend to have eosinophilic to microvacuolated cytoplasm rather than the granular, basophilic cytoplasm of a pheochromocytoma. Furthermore, adrenal cortical carcinoma tends to have a much higher mitotic index, has a trabecular pattern of growth, demonstrates fibrosis, often has larger areas of necrosis, and will have a different immunohistochemistry profile from malignant pheochromocytoma. Separation is quite difficult on core needle biopsy specimens; granular neoplasms often display diffusion artifact or “background” staining with immunohistochemical techniques, suggesting caution in overinterpreting these results on small or poorly fixed biopsies. Metastatic tumors to the adrenal gland can usually be excluded by clinical and immunohistochemical features. A malignant transformation of the sustentacular cells would mimic a malignant peripheral nerve sheath tumor (S-100 protein immunoreactive), but is a vanishingly rare possibility.8,31

**Management and Prognosis**

The treatment of choice is surgical resection (adrenalectomy), with aggressive preoperative antihypertensive management to avert a hypertensive crisis intraoperatively. Intraoperative evaluation for multicentric disease should be performed. The beneficial effect of adjuvant therapy is limited in extent to a decrease in the amount of hormone effect (partial or complete) and a reduction in the size of the tumor (either partial or complete). Overall, chemotherapy and radiation therapy (including treatment with 131I MIBG) are only of benefit in palliation by ameliorating the hypertensive effects of the excess catecholamines and not in cure or complete remission.2,3,5,9,10,32–37 However, until further studies identify precise biologic markers that can accurately predict the clinical behavior of catecholamine-secreting tumors, it is imperative to maintain lifelong clinical follow-up of patients with pheochromocytomas by both laboratory or radiologic investigation, in addition to following the patients’ symptoms at initial presentation to see if they recur.3,5,6,10,17,21,22

Pheochromocytoma usually has an excellent overall prognosis. However, pheochromocytomas are known to be capricious, occasionally demonstrating a malignant behavior years after the original resection.12 A better prognosis may be seen in patients with syndrome association or patients with bilateral tumors (although separation of these 2 groups is difficult). However, these patients frequently die of medullary thyroid carcinoma, renal cell carcinoma, or other syndrome-associated malignancies.4–8,38

By definition, malignant pheochromocytomas develop metastatic deposits, usually to the regional lymph nodes first, followed by the axial skeleton, liver, lung, and kidney.1,5,7,9,10,17,21 The usual prognosis of malignant pheochromocytoma is poor, not only related to metastatic disease but also to heart failure caused by excess catecholamines in the circulation, although highly variable in a number of patients. The overall survival ranges from 45%–55% 5-year survival.2,5,6,10,11,17,19,39

**REFERENCES**


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