Current Approach to Pheochromocytoma

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Pheochromocytomas are tumors of the neural crest-derived chromaffin cells. The hallmark of this rare and fascinating neoplasm is the synthesis and secretion of catecholamines in an unregulated and potentially life-threatening manner. Most pheochromocytomas produce an abundance of norepinephrine. Epinephrine- or dopamine-secreting pheochromocytomas are less common.[1] Pheochromocytomas can also be nonfunctional.[1] Approximately 10% of pheochromocytomas can be categorized as either bilateral, multifocal, extra-adrenal, familial, or malignant; thus, pheochromocytomas are often remembered by medical students as the "10% tumor." Newer reports, however, suggest that pheochromocytomas may be extra-adrenal in up to 30% of cases.[2,3] This brief review will address the diagnosis and management of benign and malignant pheochromocytoma.

Epidemiology
Pheochromocytomas can occur sporadically or with syndromic associations. The vast majority—approximately 90%—are believed to be sporadic. Familial syndromes associated with pheochromocytomas include multiple endocrine neoplasia (MEN) types 2A and 2B, von Recklinghausen's neurofibromatosis (NF1), and von Hippel-Lindau disease (VHL). Pheochromocytomas in patients with familial syndromes are unlikely to be malignant.[4,5] Pheochromocytomas may also accompany nonfamilial syndromes such as Sturge-Weber syndrome, tuberous sclerosis, and Carney's triad.

The genetic basis of the MEN2 syndromes has been identified as a germline mutation in the RET proto-oncogene. Germline mutations in the tumor-suppressor genes NF1 and VHL are responsible for their respectively named syndromes. In some cases of familial pheochromocytoma, somatic mutations in the succinate dehydrogenase subunit B (SDHB), C (SDHC), and D (SDHD) have been identified.[6] These advances make possible the genetic screening of individuals at risk of inheriting a pheochromocytoma related syndrome.

The incidence of pheochromocytoma is believed to be approximately 2 cases per 1 million persons per year in the United States. In hypertensive patients the prevalence is higher: 0.1% to 1%.[7] In autopsy series, a prevalence between 0.3% and 0.95% has been found.[8] In biochemical screening series, the prevalence has been reported to be as high as 1.9%.[9]

Clinical Presentation
The hallmark of pheochromocytoma is hypertension, which may occur in paroxysms against a backdrop of normal blood pressure, or the patient may have baseline hypertension with or without paroxysms of more extreme hypertension. Patients may even be identified with only occult disease (incidentaloma), or they may present with florid hypertensive crisis and multisystem organ failure. The classic triad of symptoms is relatively nonspecific and consists of headache, palpitations, and diaphoresis. Symptoms are often paroxysmal and usually last no longer than 15 minutes. Episodes have been found to increase in severity and frequency as the disease progresses.[10] When the classic triad of symptoms is found in a patient with paroxysms of hypertension, the diagnosis of pheochromocytoma is likely, and work-up must be initiated.

Biochemical Work-up
Biochemical testing should be performed on all patients who display the classic paroxysmal triad. Incidentally found adrenal tumors (incidentalomas) also require a work-up for pheochromocytoma and other functioning adrenal neoplasms. Screening tests should be considered for patients with a history of hypertension that is extraordinarily labile or unresponsive to antihypertensive therapy, new-onset hypertension during pregnancy or childhood, or a family history of pheochromocytoma or syndromes associated with pheochromocytoma (as discussed earlier). Biochemical testing should always precede localization studies.

Once pheochromocytoma is suspected, biochemical tests are used to establish the diagnosis. Fine-needle aspiration (FNA) biopsy has no role in this setting and should not be attempted for adrenal neoplasms unless pheochromocytoma has been ruled out. FNA cannot distinguish benign from malignant pheochromocytoma. This practice is very hazardous and should be strongly discouraged because it may precipitate a potentially fatal hypertensive crisis. The proper sequence of tests should be history and physical exam followed by biochemical confirmatory testing, pharmacologic adrenergic blockade, and subsequent localization.

There is no consensus on the best test for screening and diagnosis. The combination of 24-hour urinary vanillylmandelic acid (VMA) test and metanephrines has historically been used in many institutions. When either test is abnormal, the addition of confirmatory 24-hour fractionated urinary catecholamines should yield an accuracy of approximately 98%. A large number of disease states and dietary or pharmacologic substances can interfere with these biochemical studies. More detailed texts on the subject should be consulted for a complete discussion of factors leading to a misleading biochemical test for pheochromocytoma. Most patients with true pheochromocytoma have urinary catecholamine levels that are two to three times higher than the upper limit of the normal reference range. In the case of equivocal results, the clonidine suppression test may help make the diagnosis.

After the diagnosis of pheochromocytoma is confirmed by biochemical testing, the tumor should be localized and the extent of disease evaluated radiographically. Computed tomography (CT), magnetic resonance imaging (MRI), and meta-iodobenzylguanidine (MIBG) scans are complementary studies, each having its own utility in localizing these tumors. Pheochromocytomas are characteristically bright on T2-weighted images. The major advantage of MRI is the lack of exposure to radiation and IV contrast, making it the procedure of choice in pregnant women and children. The only findings consistent with malignancy on MRI or CT are local invasion of the tumor into adjacent organs or the presence of metastases. In cases where the risk of multifocality or extra-adrenal disease is low, we start with a thin-cut adrenal CT scan or MRI. If the pheochromocytoma is found by one of these studies, no further localization studies are needed. We use MIBG scanning selectively to screen for and to localize extra-adrenal, multiple, or recurrent pheochromocytomas. If necessary, an additional MRI or CT can then be used to generate more detailed images of the region with MIBG uptake. If this approach fails to localize the tumor, positron-emission tomography (PET) scanning or the use of selective venous catheterization (rarely necessary) has been useful.

Preoperative Management

Surgical removal is the only effective treatment for benign or malignant pheochromocytoma, and the likelihood of complication-free surgery is related to the adequacy of the preoperative pharmacologic and medical management. The goals of preoperative management are to normalize blood pressure, restore the vascular volume, and control dysrhythmias through alpha-adrenergic blockade and fluid administration.

The most commonly used alpha-antagonist is phenoxybenzamine (Dibenzyline). Blockade is usually initiated 1 to 3 weeks prior to surgery at a dose of 10 mg/d and increased gradually until blood pressure is controlled. Doses as high as 400 mg/d may be required. Endpoints of alpha-blockade are controlled blood pressure (< 160/90 mm Hg) or the development of side effects including reflex tachycardia, orthostatic hypotension (< 80/45 mm Hg), nasal congestion, nausea, or abdominal pain. Beta-blockers may be required for patients who develop persistent tachycardia from alpha-blockade. This class of drugs should not be used for pheochromocytoma without adequate alpha-blockade because of the possibility of precipitating hypertensive crisis from unopposed alpha-adrenergic effect.

Patients with pheochromocytoma are in a persistently vasoconstricted state, and therefore, volume repletion must accompany the pharmacologic management. Patients are encouraged to increase oral salt and fluid intake. Preoperative volume repletion is considered essential in order to avoid hypotension following the ligation of the adrenal vein. We continue pharmacologic blockade until the day of operation.
Operative Management
Complete safe surgical resection of the tumor is the goal of operative management. In the hands of experienced surgeons the laparoscopic approach is preferred whenever feasible. An open approach is preferred whenever there is evidence of malignancy, such as invasion into nearby organs or blood vessels, or for large tumor size.

The technical details of the operation will not be reviewed here, but attention should be directed to a few specific points. The entire tumor should be removed with the periadrenal fatty tissues intact, and without violation of the tumor capsule, to avoid dissemination of tumor and subsequent possible development of local recurrence or pheochromocytomatosis. Manipulation of the tumor should be limited as much as possible until after the adrenal vein is divided to avoid dangerous paroxysms of severe hypertension. Perhaps most importantly, the surgeon must maintain close communication with the anesthesia team during the entire operation, and especially at the time of adrenal vein ligation, since most patients require additional fluid and/or pressors immediately after adrenal vein division.

Postoperative Management
Three months following surgery, a 24-hour urine collection should be obtained for metanephrines to establish the patient's new baseline and ensure that there has been complete tumor removal. Weekly home blood pressure measurements should be taken for the first year and then monthly thereafter. Metastases can manifest as late as 20 years after surgery, supporting the practice of indefinite follow-up for these patients.[15] Quarterly screening for urinary catecholamine metabolites should be performed for the first year, and then screening should be done annually for at least 5 years. Changes in urinary or blood pressure measurements should prompt a work-up for metastases or contralateral primary pheochromocytoma. Pheochromocytomas also frequently secrete chromogranin A, which can be followed as a tumor marker. However, this substance may be falsely elevated with any decrease in renal function.

Malignant, Metastatic or Unresectable Pheochromocytoma
There are no agreed upon histologic characteristics for malignancy in pheochromocytoma. The presence of metastases or local invasion into surrounding tissues is the most reliable indicator. Approximately 10% to 20% of pheochromocytomas ultimately prove to be malignant. Malignancy is identified in 10% at the time of diagnosis, and approximately 5% more are identified in the ensuing 5 years.[14] Malignancy is more likely in extra-adrenal pheochromocytomas (30%-40%), larger tumors (> 6 cm), dopamine-only-secreting tumors, and with postoperative persistent hypertension.[14,16,17] The diagnosis of malignancy is best made by an imaging study showing metastases or local invasion, or these findings at operation.

The most common sites of metastases are bone (spine, skull, and ribs), liver, retroperitoneal or regional lymph nodes, lungs, and peritoneum. The median time to recurrence is between 5 and 6 years.[18] Based on data from the Surveillance, Epidemiology and End Results (SEER; 1973-2000) study, the mean survival for malignant pheochromocytoma is approximately 80 months. Other studies report 5-year survival to be between 30% and 50%.[13,14,19]

First-line therapy entails alpha-adrenergic blockade and en bloc resection of the primary tumor and resectable metastases because pheochromocytomas are relatively radioresistant and the results of cytotoxic chemotherapy have been disappointing. The combination of cyclophosphamide, dacarbazine, and vincristine or doxorubicin has been used with variable success. Therapeutic targeted radiotherapy with high-dose $^{131}$I-MIBG is being offered within experimental protocols at a few institutions. In some studies, a combination of $^{131}$I-MIBG and cytotoxic chemotherapy has been used with some success. Octreotide has been used by some investigators in an attempt to slow progression of tumor growth, but results have been mixed. External-beam radiation has been used for symptomatic metastases to the spine or long bones, or for CNS metastases.

Due to the rarity of the disease, patients with malignant or metastatic pheochromocytoma should be referred to a center with treatment expertise and, possibly, access to experimental protocols. At the time of this writing, there are currently four phase I trials and one phase II trial pertinent to malignant pheochromocytoma listed at the NCI website (www.cancer.gov). One protocol is specifically designed for malignant or metastatic pheochromocytoma, and four more are open to patients with malignant pheochromocytoma.

References:
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