CHAPTER 165 ■ PHEOCHROMOCYTOMA

DANIEL T. RUAN • QUAN-YANG DUH

IMMEDIATE CONCERNS

Major Problems

Pheochromocytoma is a rare catecholamine-secreting tumor with a wide spectrum of presentations ranging from minimal symptoms (1) to sudden death (2). Although early diagnosis can lead to a curative treatment course (3), outcomes are often fatal when the condition is unrecognized (4). Pheochromocytoma should be included in the differential diagnosis for patients with poorly controlled hypertension, heart failure, and cerebrovascular events. Furthermore, critical care physicians should be familiar with pheochromocytoma crisis, as it is a medical emergency requiring the highest level of specialty care.

Stress Points

1. The diagnosis of pheochromocytoma should be considered in any patient who presents with severe hypertension or the classic symptoms of episodic headache, palpitations, and diaphoresis.
2. Fractionated plasma metanephrines or 24-hour urine metanephrines are the initial laboratory studies to rule out pheochromocytoma.
3. α-Blockade with phenoxybenzamine should be started as soon as the biochemical diagnosis of pheochromocytoma is established.
4. After adequate α-blockade is established, β-blockers can be used as an adjuvant means of controlling tachycardia.
5. Pheochromocytoma crisis is a medical emergency requiring immediate α-blockade and invasive hemodynamic monitoring; additional pharmacologic agents, such as β-blockers, calcium channel blockers, and intravenous nitrates, are often needed to control heart rate and blood pressure.
6. The only curative therapy for pheochromocytoma is surgical resection; however, this should be attempted only on an elective basis after several weeks of adrenergic blockade.

PATHOPHYSIOLOGY

Although approximately 90% of pheochromocytomas are histologically benign, the morbidity of pheochromocytoma is primarily related to the cardiovascular impact of unregulated systemic catecholamine excess. Pheochromocytomas originate from chromaffin cells, and by definition, are located in the adrenal medulla. Although extra-adrenal pheochromocytomas are often termed paragangliomas, these terms will be considered synonymous for the purposes of this chapter.

Intermittent and unregulated catecholamine release is the hallmark pathophysiologic feature of pheochromocytoma. There are three sequential products synthesized in the adrenal medulla from the precursor L-tyrosine—dopamine, norepinephrine, and epinephrine. The rate-limiting step in catecholamine synthesis is the production of the precursor peptide L-DOPA, a process catalyzed by the enzyme tyrosine hydroxylase. By decarboxylation, L-DOPA is converted to dopamine, which is then converted to norepinephrine by β-hydroxylase. Ultimately, norepinephrine is converted to epinephrine by phenylethanolamine-N-methyltransferase.

Although norepinephrine is the predominant catecholamine secreted by most pheochromocytomas, there are reports of rare tumors that secrete dopamine (5), adrenocorticotropic hormone (6), vasoactive intestinal peptide (7), and calcitonin gene-related peptide (8). The highly varied presentation of pheochromocytoma may, in part, be explained by the variety of secretory products that have been reported. Vasoactive intestinal peptide can cause abdominal discomfort and a secretory diarrhea. Calcitonin, a gene-related peptide-like vasoactive intestinal peptide, is a potent vasodilator that can cause hypotension.

Because phenylethanolamine-N-methyltransferase is found only in the adrenal medulla and the organ of Zuckerkandl, epinephrine-secreting tumors are typically located in these two locations. Although some evidence suggests that patients in pheochromocytoma crisis have tumors that secrete primarily epinephrine, this has not been substantiated (9).

The diagnostic laboratory tests rely primarily on the detection of the metabolic products of the catecholamines. Monoamine oxidase catalyzes the conversion of catecholamines into vanillylmandelic acid and homovanillic acid. Furthermore, carboxyl-O-methyl transferase converts norepinephrine to normetanephrine and epinephrine into metanephrine.

EPIDEMIOLOGY OF PHEOCHROMOCYTOMA

Pheochromocytoma is a rare tumor with an incidence ranging from 0.1% (10) to 0.25% (11) in large autopsy studies. The prevalence in hypertensive patients is in the range of 0.1% to 1%. Pheochromocytoma can occur sporadically or in association with several familial syndromes. Although approximately 84% of cases are estimated to be sporadic (12), up to 24% of nonsyndromic pheochromocytoma patients have specific germ line mutations, including RET (MEN-2), VHL (von Hippel-Lindau), and succinate dehydrogenase subunit D (SDHD) and B (SDHB) (13).
Approximately 40% of MEN 2 patients develop pheochromocytoma. While bilateral and multicentric tumors are more common in these patients, extra-adrenal and malignant lesions are uncommon. Because of the relatively high incidence of pheochromocytoma, patients known to have the RET proto-oncogene mutation should be routinely screened for elevation in serum or urine metanephrines.

VHL disease is inherited in an autosomal dominant fashion and is characterized by retinal hemangioblastomas, kidney lesions, and epididymal cystadenomas. Pheochromocytoma can be found in up to 20% of people with VHL disease. As in MEN 2, bilateral disease is more common than in sporadic cases.

SDHB and SDHD are susceptibility genes for phaeochromocytoma associated with extra-adrenal lesions (14). Whereas SDHD mutation carriers are more likely to have multifocal extra-adrenal phaeochromocytomas, SDHB mutation carriers are more likely to develop malignancy and may be associated with kidney and thyroid cancer.

Other rare familial disorders that are associated with pheochromocytoma include von Recklinghausen disease (15) and Carney syndrome (16).

**ESSENTIAL DIAGNOSTIC TESTS**

### Biochemical Identification

The biochemical diagnosis of pheochromocytoma is dependent on the detection of elevated levels of catecholamines or their metabolites. Because functional pheochromocytomas release catecholamines heterogeneously and intermittently (25), spot checks of norepinephrine, epinephrine, or dopamine are often within a normal range and cannot reliably exclude the diagnosis of pheochromocytoma.

Conversely, free metanephrines are continuously elevated in patients with functional pheochromocytomas. Total metanephrine measurement is less sensitive than determining the fractionated amount of normetanephrine, metanephrine, and methoxytyramine, which are the metabolites of norepinephrine, epinephrine, and dopamine, respectively.

Fractionated plasma metanephrine measurement is also more sensitive than 24-hour urinary total metanephrines and catecholamines, but is less specific (26). In the critically ill patient with clinical characteristics that are highly suspicious for pheochromocytoma, measurement of fractionated plasma metanephrines is the most appropriate test. Conversely, when low-risk patients are screened, 24-hour urinary studies will yield the lowest proportion of false-positive results.

Furthermore, certain medications and radiographic contrast agents can interfere with the laboratory results and should be withheld before the draw. Clinicians should be aware of these medications, as they can affect the secretion or metabolism of catecholamines. The list of medications that can affect the biochemical testing for pheochromocytoma is long and includes the following: acetaminophen, beta-blockers, vasodilators, alpha-blockers, stimulants, antipsychotics, antidepressants, and calcium channel blockers.

In the elective setting when the diagnosis is equivocal, these medications should be withheld prior to biochemical testing. Provocative tests with agents such as histamine, glucagon, and naloxone are no longer recommended, as they can be dangerous and are ineffective in patients with normal urinary studies (27).

### Tumor Localization

Although biochemical diagnosis is essential to diagnose and start treatment for the critically ill patient with pheochromocytoma, tumor localization will not change the therapeutic plan for patients in the intensive care unit. The identification of extra-adrenal pheochromocytoma may not be predictive of malignancy or prognosis (28). However, localization studies are important for surgical planning (29) and can confirm the diagnosis.

Ultrasound is particularly useful in critically ill patients, as it can be done at the bedside without exposing them to nephrotoxic contrast agents or ionizing radiation. Although ultrasound can be performed quickly and can accurately rule out a large adrenal lesion, it can also be highly user dependent.

Magnetic resonance imaging is another effective way to identify pheochromocytoma lesions and can delineate the anatomy important for surgical planning. Pheochromocytomas
have a characteristic high-intensity signal on T2-weighted MR images. The drawbacks of MR imaging are the high cost and the lack of available scanners at some institutions. CT scanning is available at more centers than MRI or nuclear medicine studies. Although most pheochromocytomas occur in the adrenal glands, patients should be scanned from the chest to the pelvis to evaluate for extra-adrenal lesions. Drawbacks to consider include: (a) the possibility of exacerbating a pheochromocytoma crisis from contrast injection; (b) the exposure to ionizing radiation, which may be important in some pediatric or obstetric patients; and (c) the obscuring artifacts that can occur from implanted devices and surgical clips.

Metaiodobenzylguanidine (MIBG) is concentrated within adrenergic vesicles, which allow sensitive scintigraphic imaging of the whole body. It is particularly useful in patients at risk for multiple or extra-adrenal tumors, such as in young children, and in patients with a family history or familial syndrome associated with pheochromocytoma. Although MIBG scanning can localize extra-adrenal lesions, multicentric lesions, and malignant tumors with good specificity, it is less sensitive than CT or MRI.

Workup of Incidental Lesions

Subclinical or mild cases of pheochromocytoma are sometimes discovered when incidental lesions are found on CT scans or MR images obtained for other reasons. Although many clinicians continue to perform fine-needle aspiration biopsy and selective venous sampling for patients with adrenal tumors, these interventional studies may precipitate a pheochromocytoma crisis and are relatively contraindicated. The finding of an adrenal “incidentaloma” should prompt the biochemical workup described above, as well as the measurement of plasma aldosterone, renin activity, and 24-hour urine cortisol. These studies will rule out aldosteronoma and Cushing syndrome. All functioning adrenal lesions, including pheochromocytoma, should be resected electively.

MANAGEMENT

Treatment of Nonemergent Pheochromocytoma

Although pheochromocytoma is uncommon, it is a potential cause of cardiovascular emergencies such as heart failure (30), myocardial infarction (31), and stroke (32). When pheochromocytoma is the cause of these events, appropriate therapy to control the hyperadrenergic state can often reverse or minimize disability. Most patients with pheochromocytoma who succumb to myocardial infarction or cerebrovascular catastrophe have undiagnosed tumors (33).

Although surgical intervention remains the only curative therapy for pheochromocytoma, the tumor should be resected only after appropriate preoperative steps are undertaken. Preoperative preparation for elective resection includes α-blockade to control hypertension, prevent cardiac arrhythmias, and allow adequate volume resuscitation before resection. Effective preoperative preparation and α-blockade reduces operative mortality (34). Even in the normotensive patient, complete α-blockade will prevent hemodynamic instability caused by operative stress and tumor manipulation during elective resection.

Phenoxybenzamine is an ideal α-blocker for preoperative patients because it has a relatively long half-life. The starting dose is 10 mg every 12 hours and should be titrated upward, as tolerated. The highest tolerable level of blockade is preferable, and dose escalation can be halted when the patient has postural hypotension. Most patients complain of nasal congestion during adequate α-blockade, but this need not prompt adjustment in dosage.

β-Blockers are sometimes needed to control heart rate before the resection. They should be given only after adequate α-blockade, to avoid severe hypertension from unopposed α-stimulation. Metoprolol, an inhibitor of tyrosine hydroxylase, reduces catecholamine production and can be added to the preoperative regimen (35). Narcotics should generally be avoided, as they may stimulate histamine release, which may in turn trigger a crisis.

Although surgical resection is the only curative intervention for patients with pheochromocytoma, appropriate preoperative measures help to avoid unfavorable events, such as intraoperative hemodynamic instability. α-Blockade must be attained before elective resection of pheochromocytoma. β-Blockade is used selectively in patients with persistent tachycardia, but only after adequate α-blockade.

Managing the Postoperative Patient

Perioperative complications are either related to inadequate adrenergic blockade, lack of appropriate intravascular volume expansion, or to a technical problem. Surgical complications include bleeding, infection, and damage to nearby structures, such as the spleen or renal vessels.

Most pheochromocytomas smaller than 6 cm can be resected using the laparoscopic technique. Larger tumors may require laparotomy or thoracobdominal access for safe resection. Despite preoperative α-blockade, many patients have either arrhythmias or some form of hemodynamic instability during adrenalectomy. Some compensatory hypotension often results after tumor extirpation. Typically, this drop in blood pressure is minimized when blood volume is restored appropriately and when α-blockade is adequate preoperatively. Sometimes, intravenous boluses of crystalloids and colloids, or catecholamines, are required to maintain blood pressure after resection.

Although many patients with pheochromocytoma are hypoglycemic before resection, because of chronic catecholamine excess, they may be profoundly hypoglycemic in the early postoperative period. Intravenous glucose and frequent blood sugar checks are required in many of these patients.

Essential hypertension may persist after resection. Disease may recur from the contralateral adrenal gland or metastases years after surgery. Reoperative resection is the treatment of choice when complete extirpation is feasible. Furthermore, palatoveal debulking is often desirable in patients with disease that cannot be completely resected, as it can improve symptoms and the effectiveness of medical therapy. An uncommon surgical complication of adrenalectomy is renovascular hypertension, a result of injury to, or thrombosis of, the renal artery or vein.
**Treatment of Pheochromocytoma Crisis**

Pheochromocytoma crisis is an uncommon event that requires prompt diagnosis and emergent medical intervention. The clinical presentation of pheochromocytoma crisis includes (i) multisystem organ failure; (ii) fever, often exceeding 40°C; (iii) encephalopathy; and (iv) hemodynamic instability (36). A common error is the misdiagnosis of sepsis in patients whose condition continues to decline despite empiric antibiotic therapy.

Episodes of pheochromocytoma crisis are typically precipitated by traumatic stress, which is often iatrogenic. Furthermore, crises usually develop in undiagnosed or untreated patients without -blockade. Patients in pheochromocytoma crisis should be transferred urgently to an intensive care unit, or to the highest level of care available.

Phentolamine, an intravenous -blocker, should be given in 2-mg boluses. Larger doses can result in hypotension. Phenylephrine and prazosin can also be used but can be more difficult to titrate. -Blockade, without -blocker, can precipitate hemodynamic instability, as unopposed -stimulation can cause peripheral vasoconstriction (37). However, after initial -blockade is started, -blockade can effectively control heart rate and blood pressure. Labetalol, which has both - and -blocker effects, can be given intravenously during crisis situations.

Other useful medications include nitrates, such as sodium nitroprusside and nitroglycerine. These agents result in prompt vasoconstriction, which can decrease cardiac preload and cause an immediate decline in blood pressure. Side effects from sodium nitroprusside include cyanide accumulation after long-term use. Ultimately, these agents should be used as adjuvant therapies after -adrenergic blockade is achieved.

Ideally, real-time arterial pressure should be monitored with the placement of a radial artery arterial line. Measurement of urinary output with a bladder catheter is simple, quick, and useful. Central venous monitoring is not an essential component in the initial care of patients in pheochromocytoma crisis, and central venous catheter placement should not delay pharmacologic treatment. However, many pharmacologic agents require central venous delivery, and central venous catheters are useful for monitoring volume status.

Emergent adrenalectomy should be avoided in patients with pheochromocytoma crisis. After the patient is stabilized and -blockade instituted, planning should begin for elective adrenalectomy with curative intent. This can be performed during the same admission after preoperative planning, including the completion of localization studies and at least 2 weeks of -blockade.

**Pregnancy and Pheochromocytoma**

The stress of pregnancy and labor can prompt pheochromocytoma crisis and elicit symptoms in patients with unrecognized pheochromocytoma (38). On rare occasions, symptoms are minimal during gestation and manifest only after delivery (39). Obstetric outcomes are exceptionally poor when maternal pheochromocytoma is unrecognized; fetal and maternal mortality rates exceed 50% in such cases (40). However, others have reported favorable results when the diagnosis is established and the mother is adequately treated antenatally (41). Although the presenting symptoms and the biochemical workup are no different in obstetric patients, maternal hypertenison is often erroneously attributed to pre-eclampsia or eclampsia. Because of the grave consequences related to this missed diagnosis, pheochromocytoma should be considered in any hypertensive gravid woman.

The localization of pheochromocytoma lesions in pregnant women should avoid fetal exposure to ionizing radiation. Ultrasound and MRI are safe, but CT and MBG scanning result in some fetal exposure to radiation.

Both - and -blockade can be given safely in the obstetric patient. The timing of surgical resection should be carefully planned. Emergent adrenalectomy is not required and should be delayed until delivery, which should be accomplished by cesarean section, or thereafter. If the diagnosis is made early in the gestational period and medical therapy is poorly tolerated, the second trimester is the ideal time period for elective laparoscopic resection. Surgery in the first trimester is associated with fetal loss, and resection in the third trimester can be technically challenging because of the larger uterus, and can cause premature labor.

**SUMMARY**

The diagnosis of pheochromocytoma should be considered in any patient with the classic symptoms of headache and diaphoresis with severe hypertension. Furthermore, pheochromocytoma should be included in the differential diagnosis in any patient with an unexplained cardiovascular event, including congestive heart failure, myocardial infarction, or stroke. The cornerstone of diagnosis is biochemical evaluation by either plasma-fractionated metanephrines or 24-hour collection of urine metanephrines. Pheochromocytoma crisis is a medical emergency that is often misdiagnosed as severe sepsis. Clinical outcomes are uniformly fatal when pheochromocytoma is undiagnosed. The initial therapy includes -blockade titrated to orthostatic hypotension. Both -blockade and intravenous nitrates are useful adjuvant therapies to control tachycardia and hypertension, respectively. Ultimately, curative outcomes depend on complete surgical resection, which is most safely performed after a 2-week period of -blockade and subsequent reevaluation.

**References**

CHAPTER 166 ■ THYROID DISEASE IN THE INTENSIVE CARE UNIT

JENNIFER A. SIPOS • WILLIAM G. CANCE

The purpose of this chapter is to discuss thyroid disease as it may present in an intensive care unit (ICU). Interpretation of thyroid function tests in a critically ill patient requires knowledge of the perturbations of hormone synthesis that may occur with illness and certain medications. This text will also discuss the diagnosis and treatment of thyroid emergencies: myxedema coma, thyroid storm, postthyroidectomy hypocalcemia, and airway obstruction by goiter.

THYROID FUNCTION TESTS

There are a myriad of tests that may be ordered to evaluate thyroid function, so finding the right test or set of tests can compound the complexity interpreting these values once they are obtained. The purpose of this section is to provide an overview of the most commonly ordered labs. A later section will delineate how to interpret these values in the critically ill patient.

Measurement of serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) is sufficient to diagnose most thyroid disorders. It is recommended to use the now widely available ultrasensitive TSH (1). The normal reference range for this test