neurofibromatosis, cerebelloretinal hemangioblastosis (von Hippel–Lindau disease), and tuberous sclerosis.

Clinical Presentation

Because most pheochromocytomas secrete norepinephrine as the principal catecholamine, hypertension (often paroxysmal) is the most common finding. Other symptoms include the triad of headache, palpitations, and sweating as well as skin blanching, diarrhea, anxiety, nausea, fatigue, weight loss, and abdominal and chest pain. Emotional stress, exercise, anesthesia, abdominal pressure, or intake of tyramine-containing foods may precipitate these symptoms. Orthostatic hypotension can also occur. Wide fluctuations in blood pressure are characteristic, and the hypertension associated with pheochromocytoma usually does not respond to standard antihypertensive medicines. Cardiac abnormalities, as well as idiosyncratic reactions to medications, may also occur.

Diagnosis and Treatment

Although measurements of fractionated catecholamine and metanephrine levels in the urine are often used as screening tests, plasma free metanephrine and normetanephrine levels are the best tests for confirming or excluding pheochromocytoma. A plasma free metanephrine level greater than 0.61 nmol/L and a plasma free normetanephrine level greater than 0.31 nmol/L are consistent with the diagnosis of a pheochromocytoma. If these levels are only mildly elevated, a clonidine suppression test can be performed. In patients with pheochromocytoma, levels are unchanged or increased. Once the diagnosis of pheochromocytoma is made, a CT scan of the adrenal glands should be performed. Most intra-adrenal pheochromocytomas are readily visible on this scan and enhance with contrast. If the CT scan is negative, then extra-adrenal pheochromocytomas can often be localized by iodine 131–labeled metaiodobenzylguanidine (^{131}I-MIBG), positron emission tomography, octreotide scan, or abdominal MRI. Pheochromocytomas show high signal intensity on T2-weighted images.

The treatment of pheochromocytoma is surgical if the lesion can be localized. Patients should undergo preoperative α-blockade with phenoxybenzamine 1 to 2 weeks before surgery. β-Adrenergic antagonists should be used before or during surgery. About 5% to 10% of pheochromocytomas are malignant. ^{131}I-MIBG or chemotherapy may be useful, but the prognosis is poor. α-Methyl-*p*-tyrosine, an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis, may be used to decrease catecholamine secretion from the tumor.

Incidental Adrenal Mass

Clinically inapparent adrenal masses may be discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions not related to the signs and symptoms of adrenal disease; they are commonly known as *incidentalomas* (E-Fig. 64-2). Some of these tumors secrete a small amount of excess cortisol, leading to a condition called *subclinical Cushing's syndrome*. A morning plasma ACTH level and an overnight 1-mg dexamethasone test are recommended for patients with an adrenal incidentaloma. Patients with hypertension should also undergo measurement of serum potassium, plasma aldosterone concentration, PRA, and urine or plasma free metanephrines. Surgery should be considered for all patients with functional adrenal cortical tumors that are hormonally active or larger than 4 cm. Tumors not associated with hormonal secretion that are smaller than 4 cm can be monitored with repeated imaging and hormonal assessment.

Primary Adrenal Cancer

Primary adrenal carcinomas are rare, with an incidence of 1 to 5 per 1 million persons. The female-to-male ratio is 2.5 : 1, and the mean age at onset is 40 to 50 years. About 25% of patients have symptoms, including abdominal pain, weight loss, anorexia, and fever. Eighty percent of primary adrenal carcinomas are functional, with secretion of glucocorticoid alone (45%) or glucocorticoid plus androgens (45%) being most common.

At presentation, metastatic spread is evident in 75% of cases. An incidentally discovered adrenal mass that is large is more likely to be malignant. Resection is recommended for tumors larger than 6 cm and often for those larger than 4 cm. In patients who do not have a known cancer, most adrenal masses that turn out to be malignant are primary adrenocortical carcinomas, whereas in patients with a known malignancy, an adrenal mass is likely to be a metastasis in about 75% of cases.

The treatment of adrenocortical carcinomas is surgery. These cancers are usually resistant to radiation and chemotherapy, but the adrenolytic compound mitotane has been shown to improve survival. Adrenocortical carcinomas carry a poor prognosis, with overall 5-year survival rates of less than 20%.

For a deeper discussion on this topic, please see Chapter 227, "Adrenal Cortex," in Goldman-Cecil Medicine, *25th Edition.*

SUGGESTED READINGS

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