The Incidentally Discovered Adrenal Mass

PAUL M. COPELAND, M.D.

Editor's comment: This is the fourth in a series of papers being exchanged by *ANNALS OF INTERNAL MEDICINE* and *ANNALS OF SURGERY* for republication with the view that specially selected subjects will be of considerable interest to the readers of these journals and are exchanged accordingly.

With the wider application of increasingly sensitive computed tomographic scans, more adrenal masses will be discovered incidentally. Because benign lesions of the adrenal are much commoner than malignant ones, an approach is needed to determine which incidentally discovered masses should be removed. The history and physical examination may guide the evaluation. Imaging studies and needle biopsies have limited value. If the history and physical findings do not suggest a diagnosis, an approach using the size of the mass, results of any cyst puncture, and a biochemical assessment may determine which patients should have surgery. This approach is based on the relative prevalence of benign and malignant clinically silent adrenal tumors.

DIAGNOSTIC PROCEDURES may yield incidental findings that then require further definition. The incidentally discovered adrenal mass poses such an issue. Within the span of 1 month at the Massachusetts General Hospital, we were faced with the evaluation of three patients who had adrenal masses incidentally discovered on intravenous pyelography. Such masses will be detected even more frequently with the wider application of increasingly sensitive computed tomographic (CT) scans. Unsuspected adrenal masses have been detected on 0.6% of upper abdominal CT studies.[1,2] Among 51 reported patients with adrenal masses incidentally discovered on CT scan, three had a clinically unsuspected, biochemically active pheochromocytoma.[1-4] The rest of the masses proved to be lesions for which surgery would not be needed: 15 metastases from known malignancies, 12 clinically and biochemically silent cortical adenomas, five cysts, one focal cortical hyperplasia, one lipoma, one myelolipoma, one "nonfunctioning" pheochromocytoma, one surgically shown neoplasm of the pancreatic tail rather than an adrenal mass, and 11 patients followed without changes on subsequent CT scans or referrable clinical findings.[1-4]

Our treatment approach should be guided by the high prevalence of benign, clinically silent, adrenal adenomas (from autopsy series, 1.4% to 8.7%),[5-8] compared with the rarity of occult nonfunctioning adrenocortical carcinoma (annual incidence from cancer registries of all adrenocortical carcinoma of 0.0006% to 0.00017%).[9,10] If we do not manage these masses appropriately, we may create an iatrogenic disease of medical progress.

Adrenal masses in the adult may be cortical adenomas, cortical carcinomas, pheochromocytomas, ganglioneuromas, cysts, myelolipomas, adenolipomas, or metastases from other tumors.[11] When an adrenal mass is found, the following questions arise: Is it hormonally active and likely to produce detrimental symptoms on that basis; and is it a primary adrenal malignancy? If the mass produces hormones in sufficient quantity to cause symptoms, it should be removed, whether it is a cortical adenoma, carcinoma, or pheochromocytoma. If inactive and not malignant, the mass may be left in place. The difficulty is that cortical carcinomas may produce manifestations of hormonal excess or they may be putative "nonhormonal" or "nonfunctional" carcinomas.

Nonfunctional carcinomas may constitute a smaller proportion of adrenocortical carcinomas than previously thought. When the urinary steroid excretions of patients with clinically "nonfunctional" carcinomas are examined, many are actually producing adrenal steroids in excess. In two series in which urinary 17-ketosteroids were measured, 8 of 12 patients with presumed nonfunctional adrenocortical carcinomas were excreting increased amounts of the steroids.[12,13] In various series, clinically "nonhor-

From the Endocrine Unit, Medical Services, and the Department of Neurology, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School; Boston, Massachusetts

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Reprint requests: Paul M. Copeland, M.D., Endocrine Unit, Massachusetts General Hospital, Boston MA 02114.

monal" or "nonfunctional" adrenocortical carcinomas comprised 4% to 76% of cases of adrenocortical carcinoma[13–21]; the proportion is 30% to 50% in most series. An ascertainment bias probably accounts for the wide discrepancies. The low figures are generally compiled by endocrinologists. The extreme low figure is from a series studying o,p'DDD, a steroid synthesis blocker, as a therapy.[14] The high proportion figures for nonfunctioning carcinomas represent data collected by surgeons and pathologists. The highest value is from a cancer institute study in which 18 of the 42 patients were diagnosed postmortem.[15] In general, when steroid production is subject to greater scrutiny, the proportion of "nonhormonal" adrenocortical carcinomas decreases.

Evaluation of the Adrenal Mass

Determination of biochemical activity is a fundamental consideration in the assessment of adrenal masses. Other potentially decisive factors are the age and sex of the patient, the size of the mass, its imaging characteristics, and its cytologic features.

With regard to biochemical activity, the first tool is the history and physical examination: a search for evidence of Cushing's syndrome, virilization, feminization, mineralocorticoid excess, and catecholamine excess. Any patient with clinical evidence for one of these conditions should be evaluated in the usual manner. A primary adrenal malignancy may show evidence of local extension or distant metastases, most commonly to lung, liver, lymph nodes, peritoneum, bone, and pleura.[15,22] The examiner should also consider the possibility of metastases to the adrenal gland from nonadrenal malignancies.

Laboratory Assessment

The laboratory assessment of a patient with an adrenal mass should include a 24-hour urine collection for 17-hydroxycorticosteroids and 17-ketosteroids. Excretion of 17-ketosteroids is especially important in the search for adrenocortical carcinoma; 17-ketosteroids can be elevated with normal 17-hydroxycorticosteroids. In one series of 22 patients with elevated urinary 17-ketosteroids, 3 had normal urinary 17-hydroxycorticosteroids.[13] Elevated urinary 17-hydroxycorticosteroid excretion may be seen in patients with adrenocortical carcinoma in the absence of clinical Cushing's syndrome.[23] Such an elevation has been associated with relative inactivity of the enzyme 11β-hydroxylase.[23] The inefficiency of this enzyme causes an increase in the secretion of 11-deoxycortisol and therefore of urinary tetrahydro-11-deoxycortisol, which is detected by the standard assay for urinary 17-hydroxycorticosteroids. Thus, urinary 17-hydroxycorticosteroids can be elevated with a normal plasma cortisol level.[24]

In addition to measurement of the basal steroid excretion, a low-dose dexamethasone suppression test (0.5 mg orally every 6 hours for 2 consecutive days) should be done to show normal suppressibility of the urinary steroids. Alternatively, one could proceed directly to a high-dose dexamethasone suppression test (2 mg orally every 6 hours for 2 consecutive days) because pituitary-dependent Cushing's disease need not be considered. Several cases have been reported of adrenocortical tumors in which the basal steroid excretion was within normal limits but failed to suppress normally after dexamethasone administration.[13,25]

Plasma testosterone levels should be measured only if there is any sign of hirsuitism or virilization in a woman or a child. Testosterone may occasionally be elevated without elevation of the precursor 17-ketosteroids. Among 18 cases of virilizing adrenal adenoma where plasma testosterone and urinary 17-ketosteroid levels were measured, testosterone concentration was elevated in three women who had normal 17-ketosteroid values.[26] In men with adrenal tumors, however, elevation of plasma testosterone levels above the normal range is unknown without elevation of urinary levels of 17-ketosteroids. Similarly, estrogen levels need to be measured only if feminization is detected in a man or a child. In a review of feminizing adrenal tumors, levels of 17-ketosteroids were elevated in all but 5 of 24 patients with carcinoma in which they were measured.[27]

The enzymatic machinery of an adrenocortical carcinoma may be inefficient; the consequences of relative 11β-hydroxylase deficiency have already been considered. If the enzymatic inefficiency involves 3β-hydroxysteroid dehydrogenase-isomerase, 21-hydroxylase, and 17-20 desmolase, an adrenocortical carcinoma can produce excess pregnenolone without an elevation of 17-hydroxycorticosteroid or 17-ketosteroid levels. These findings have been observed in some patients with supposedly "nonfunctional" adrenocortical carcinomas. These patients had markedly elevated excretion of a pregnenolone metabolite, pregn-5-ene-3α,16α,20α-triol, without elevated urinary 17-ketosteroids.[12,28,29] Urinary 17-ketogenic steroids were also elevated in each of these reported cases. The conventional assay for ketogenic steroids measures steroids with a 21-deoxy, 20-keto, 17-hydroxy side chain; therefore, 17-hydroxyprogesterone and its metabolite, pregnanetriol, are measured by this test, although they would not be measured as 17-hydroxycorticosteroids or 17-ketosteroids. Thus, one can assay for the pregnenolone metabolite directly or measure the urinary 17-ketogenic steroids in the evaluation of the patient with an adrenal mass.

Aldosterone excess is rare in adrenocortical carcinoma. In a literature review,[30] published in 1969, only 11 cases had been found. In 10 of these 11 cases, urinary 17-hydroxycorticosteroid and 17-ketosteroid levels were also abnormal. In the one reported case in which 17-hydroxycorticosteroid and 17-ketosteroid levels were normal, they were measured only once; moreover, aldosterone excretion was not measured. The diagnosis was based only on hypertension and a hypokalemic alkalosis.[31] Although a pure mineralocorticoid-secreting adrenocortical carcinoma is extremely rare, a benign aldosteronoma must be considered in the differential diagnosis. Most patients with mineralocorticoid excess have hypertension and hypokalemia; however, the basal potassium may be normal.[32] Hypertensive patients with an incidentally discovered adrenal mass should be screened for occult mineralocorticoid excess. A reasonable test would be the measurement of serum potassium while the patient is on a moderately high (200 meq or more) sodium diet.[33] Most patients with primary hyperaldosteronism become hypokalemic on this regimen, whereas, in normal subjects, serum potassium levels do not significantly change.

In contrast to aldosteronomas, clinically unsuspected pheochromocytomas can be both elusive and potentially lethal. A recent 50-year autopsy series from the Mayo Clinic[34] described 41 patients with clinically unsuspected pheochromocytoma. Only 54% had a recorded history of hypertension. Thus, the absence of hypertension does not exclude the diagnosis of pheochromocytoma in a patient with an incidentally discovered adrenal mass. The search for a pheochromocytoma should use some combination of 24-hour urine for vanillylmandelic acid, metanephrines, and catecholamines. In one series, each measurement was more than 95% sensitive.[35] In another series,[36] however, of 23 patients with pheochromocytoma, three had normal vanillylmandelic acid and metanephrines measurements but elevated catecholamines. A 24-hour urine collection for measurement of vanillylmandelic acid or metanephrines should suffice for patients with an asymptomatic adrenal mass. The metanephrine assay is preferred because it has greater specificity than the commonly used vanillylmandelic acid assay.[37] If doubt persists, a collection for metanephrines can be repeated and urinary epinephrine and norepinephrine values can be measured. Any positive result on these screening tests needs further confirmation before surgery.

Clinical Features

In most series of patients with Cushing's syndrome caused by adrenocortical carcinoma, women outnumber men approximately sixfold.[13,23] Among clinically nonfunctional carcinomas, however, there are twice as many men as women.[13,23] Older patients have a higher incidence of endocrinologically silent carcinomas. Nonfunctional adrenocortical carcinomas are relatively rare among children. In a cumulative tally of seven series, 5 of 29 patients under age 20 years had endocrinologically silent carcinomas, whereas 89 of 151 patients over age 20 years were in that category.[13,15,16,18-21]

Imaging Characteristics

The size of the mass is perhaps the most helpful determinant of the nature of a biochemically silent lesion. Adenomas 6 cm or larger in diameter are rare (3 in 12000 autopsies);[5-8] however, adenomas of up to 10.5 cm have been reported in autopsy series.[5] At the Massachusetts General Hospital, an incidentally discovered mass measuring 11- × -10- × -6.5-cm proved to be a benign adenoma both histologically and clinically. Adrenal cysts occasionally may attain very great dimensions.[38] In contrast, most adrenocortical carcinomas are over 6 cm in diameter. Among six series, 105 of 114 adrenocortical carcinomas were over 6 cm in diameter.[12,13,18-20,39] A smaller lesion, however, should not be totally ignored. The size of the removed carcinoma may be inversely related to the prognosis. In three large series in which follow-up data were presented, all five patients with nonmetastatic adrenocortical carcinoma removed when smaller than 5 cm survived at least 5 years, whereas only 6 of 54 patients with larger lesions or metastases survived longer than 5 years.[19-21]

Because survival may be improved when carcinomas are removed while they are small, it would be advantageous to identify and operate on the patients with small nonfunctioning carcinomas. Unfortunately, aside from the biochemical determinations, the available methods (that is, imaging techniques and needle aspiration) do not generally distinguish malignant from benign lesions. Among imaging techniques, the plain film of the abdomen has little value. Although calcification is commonly thought to signal malignancy, it can follow local hemorrhage into both malignant and benign lesions.[40] In one series, 6 of 11 benign cysts were calcified.[41] The intravenous pyelogram is capable of detecting lesions larger than 2 to 3 cm in diameter but adds little in definition.[42] The CT scan offers the most promise: Decreased attenuation coefficients can generally distinguish cystic from solid lesions, but the lipid content can give low-density areas, which can be mistaken for cystic lesions.[43] Contrast enhancement is valuable for better definition of a cyst. Ultrasound has been useful in thin patients who have little fat to outline structures on computed tomography.[44] Angiography is not specific in the diagnosis of adrenal

masses. Neovascularization and arteriovenous shunting may be present or absent in both adenomas and carcinomas.[45] Advantages of angiography are that the blood supply of the lesion may help define its organ origin and that an avascular mass may suggest the presence of a cyst. Although low uptake with radiocholesterol scanning will usually differentiate adrenocortical carcinomas from cortisol- or aldosterone-secreting adenomas,[46] low uptake cannot be equated with malignancy in biochemically silent adrenal masses. Biochemically silent adrenal adenomas have not been extensively studied with radiocholesterol scanning; one study reported localization by increased uptake of iodocholesterol in four of ten patients.[47] Further research is needed to assess the natural history of such adenomas. The lower uptakes in most patients with biochemically silent masses may be predicted from the correlation of uptake with secretory activity.[48]

Fine Needle Aspiration

Fine needle aspiration of an adrenal mass has a limited role. It is most helpful in the differential diagnosis of a cystic mass. Clear fluid is uniformly associated with a benign lesion. Bloody fluid may be either benign or malignant. In a small series, Scheible and associates[38] showed the utility of cyst puncture in obtaining clear fluid in two of three lesions. Cysts of the adrenal gland may be grouped in four categories, with the occurrence among 155 cases reviewed by Abeshouse and colleagues[49] indicated in parentheses: echinococcal parasitic cysts (6%); retention cysts (2%), which are embryonal in origin; cystic degenerative adenomas (7%); endothelial cysts (44%), which are more commonly lymphangiomatous than angiomatous; and pseudocysts (39%), which are formed by hemorrhage into normal or pathologic glands (cysts of unstated type constituted 2%). In a series of 11 cysts described by Kearney and coworkers,[41] all proved to be variations of pseudocysts: three were cystic pheochromocytomas and eight were the result of hemorrhages into normal glands. None were malignant. Therefore, a bloody aspirate does not necessarily indicate malignancy.

Cytologic evaluation of fine needle aspirates holds little promise in distinguishing benign from malignant lesions because of the difficulty in the cytologic definition of malignancy. Extreme examples of benign and malignant lesions can be differentiated. In many adrenal adenomas, tumor cells closely resemble the normal cortex. Carcinomas, on the other hand, tend to have nuclei that are hyperchromatic and pleomorphic. Carcinomas can also show numerous mitoses and bizarre forms. In a series of 23 benign lesions, none had more than five mitotic figures per high-power field (hpf).[19] Of 13 malignant lesions, seven had more than five mitoses/hpf. Therefore, a large number of mitoses is a specific but not sensitive indicator of malignancy. More reliable diagnostic features of carcinomas are invasions through the capsule and into veins.[18] Discernment of capsular and venous invasion, however, is not possible from fine needle cytologic examination. Fine needle aspiration has been used successfully in a case of adrenocortical carcinoma.[50] The cells showed apposition of the nuclear and cytoplasmic membranes and variably shaped nuclei in multinucleated cells. Given its limitations, the technique cannot be generally recommended for the evaluation of an incidentally discovered adrenal mass.

Approach to the Adrenal Mass

Few of the available means for distinguishing malignant from benign lesions without surgery are of value. Biochemical activity, although a specific marker for tumors requiring surgery, is not sufficiently sensitive. Adult age and male gender also fail to distinguish reliably a nonfunctional carcinoma from a benign lesion. The size of the mass is quite helpful, although not all lesions larger than 6 cm in diameter are carcinoma, nor, certainly, are all smaller lesions benign. Imaging characteristics are not very helpful: Calcification does not indicate malignancy, nor does nonhomogeneity on CT scanning. Irregular borders may suggest malignancy when they are discernible.[4] A cystic lesion may be approached with cyst puncture and be considered benign if the fluid is clear; however, if the fluid is bloody, benign and malignant lesions cannot be distinguished.

To determine which patients should undergo surgery, we need to assess the likelihood that a patient will have a nonfunctional adrenocortical carcinoma. Tumor registries suggest that the annual incidence of all adrenal gland malignancies is 1 per 400,000.[9] This figure includes malignant neuroblastomas and pheochromocytomas. Neuroblastomas present as large lesions in childhood. Biochemically silent, malignant adrenal pheochromocytomas have never been reported. Neither of these lesions would enter the differential diagnosis of incidentally discovered, biochemically silent adrenal masses in adults. Adrenocortical carcinomas have an annual incidence of 1 per 600,000 to 1 per 1.6 million.[9,10] Biochemical activity can be detected in at least two thirds of patients with adrenocortical carcinoma. Therefore, even using the higher incidence figures, the annual incidence of biochemically silent adrenocortical carcinoma is approximately 1 per 1.8 million. If the duration of clinically inapparent, adrenocortical carcinoma is assumed to be even as long as 7 years,[15] the prevalence of biochemically silent adrenocortical carcinoma would be less than 1 per 250,000. In contrast, benign clinically inapparent adenomas of the

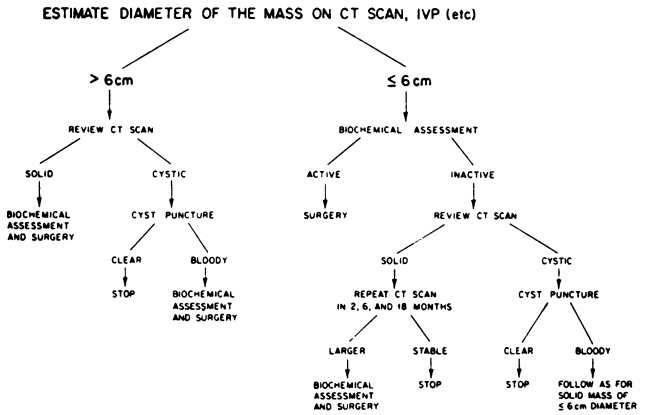

FIG. 1. Approach to the incidentally discovered adrenal mass. The diameter of the mass can be estimated using the radiologic method by which it is detected. Biochemical assessment should include 24-hour urine measurement of metanephrines (or vanillylmandelic acid), 17-hydroxycorticosteroids, and 17-ketosteroids (and 17-ketogenic steroids if 17-hydroxycorticosteroids and 17-ketosteroids are normal); a low-dose dexamethasone test to show normal suppressibility of the urinary steroids; and in hypertensive patients, serum potassium while the patient is on a diet with more than 200 meq of sodium and less than 100 meq of potassium. IVP = intravenous pyelogram.

adrenal are quite common. In four large autopsy series the prevalence and size range of adrenal adenomas have been reported. Russi and associates[6] found adenomas in 1.45% of 9000 patients autopsied; Shamma and colleagues,[5] 1.8% of 220; Kokko and co-workers,[7] 1.41% of 2000; and, in the only prospective study, Hedeland and associates[8] found 8.7% of 739. The sizes of the adenomas ranged up to 4 cm in one series,[8] 6 cm in two[6,7] and 10.5 cm in the fourth.[5] In the total experience of 12,000 autopsies in these four studies, thee were three adenomas of 6 cm in diameter or larger. The prevalence of adenomas of this size, therefore, is approximately 1 per 4000. If the prevalence of biochemically silent adrenocortical carcinoma is about 1 per 250,000, over 60 operations would have to be done on patients with adrenal masses of 6 cm in diameter or larger to remove one carcinoma. Smaller adenomas are much commoner. Operations for smaller masses would remove carcinomas much less often. Using the data of Shamma and colleagues,[5] in which the prevalence of adenomas 1.5 cm in diameter or larger was 1 per 56, over 4000 operations would have to be done on patients with masses 1.5 cm in diameter or larger to remove one carcinoma. The complication rate from adrenalectomy is such that the overall morbidity and mortality would be greatly increased by operating on all adrenal masses less than 6 cm in diameter. In three large series of unilateral adrenalectomy done since 1974 for an aldosteronoma (the adrenal lesion with the most benign perioperative course), among a total of 36 patients the morbidity was 42%.[51-53] There was no mortality arising from these recent operations, but an overall mortality of more than 10% was reported for earlier operations. Presumably, the complication rate is higher in less expert hands.

Glazer and co-workers[1] have suggested that biopsy or excision of all adrenal masses larger than 3 to 4 cm in diameter "be considered." Their own series of 16 incidentally discovered adrenal masses contained one benign mass 6 cm in diameter and no malignant lesions. They do not present evidence to support the "3- to 4-cm" criterion. Prinz and associates[2] have suggested an even more aggressive approach; they recommend that patients with an incidentally discovered adrenal mass who are younger than 50 years or with a lesion greater than 3 cm in diameter should undergo surgery even if excess hormone production is not demonstrable. The criterion of a 3-cm diameter lesion was selected without documentation. The age criterion was based on the finding by Dobbie[54] of a higher average age among autopsied patients with benign nodules than among those with normal adrenal glands (49.5 years "normal," 60 years "mild nodularity," 65 years "distinct nodularity"). No statistics were applied to test the significance of the difference. Further, in other studies, the incidence of nonfunctional adrenocortical carcinoma was lower among younger persons.[13,15,16,18,20,21] Thus, age under 50 years should not be a criterion for surgery. If the criteria of Prinz and colleagues[2] were applied, surgery would still be recommended for four of the nine patients with incidentally discovered adrenal masses in their own series. Only one of these four patients proved to have a clinically important adrenal lesion. By using the recommendations given below, only the patient with a clinically important lesion would have had surgery.

Recommendations

Figure 1 illustrates an approach to the incidentally discovered adrenal mass in adults. Benign large adenomas (defined as greater than 6 cm in diameter) have been reported only once among 12,000 autopsies. Most lesions of adrenocortical carcinoma are larger than 6 cm in diameter when initially detected.[12,13,18-20,39] Therefore, large masses that are solid on CT scan should be operated on after a biochemical assessment to search for disease activity and to provide a baseline evaluation. The biochemical assessment should include 24-hour urine measurements of metanephrines (or vanillylmandelic acid), 17-hydroxycorticosteroids, 17-ketosteroids, and 17-ketogenic steroids (if 17-hydroxycorticosteroids and 17-ketosteroids are normal). A low-dose dexamethasone suppression test should be done to evaluate normal suppressibility of the 17-hydroxycorticosteroids. If the patient

has hypertension, serum potassium should be measured on a high-sodium (200 meq or more), low-potassium (less than 100 meq) diet.

If a large mass is cystic on CT scan, a cyst puncture should be done. Clear fluid can be assumed to indicate a benign lesion. Bloody fluid does not necessarily augur malignancy but a large bloody cyst merits biochemical assessment and surgery as for a solid mass.

If the mass is small (6 cm or less in diameter), a biochemical assessment is indicated. If biochemical activity is confirmed, the lesion should be removed. If it is inactive, a mass that is cystic on CT scan may be punctured; however, sharply marginated, round, homogeneous water density cysts may be assumed to be benign.[4] Clear fluid obtained by puncture would confirm the presence of a benign lesion; bloody fluid warrants the same approach as for a solid mass of similar size. Needle aspiration of a small solid mass may be considered; however, as the sensitivity of cytologic examination would be only 54%[19] and the incidence of adrenocortical carcinoma among persons with small masses is less than 1 per 60, the likelihood of positive cytologic findings is less than 1%. Small blood cysts and small solid masses may be followed for a change in size by serial CT scans. The recommended intervals of 2, 6, and 18 months are based on an estimate of the range of doubling time for adrenocortical carcinomas.[18] If the mass increases in size at any re-evaluation, biochemical assessment should be repeated and surgery should be done. If the mass size is stable after 18 months, it may be left in place. This approach may be modified by future experience. For now, it should prevent a substantial number of unnecessary operations.

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