CLINICAL VIGNETTE

Adrenal Incidentaloma

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A 70-year-old obese woman with diabetes, hypertension, and chronic abdominal pain of undetermined etiology was referred for management of her diabetes mellitusa. A CT scan to evaluate her abdominal discomfort revealed a previously unsuspected right adrenal nodule (36 x 39 mm, 34 x 40 on repeat scan years later and Hounsfield units of 20). When this issue was brought to the patient's attention, she declined further evaluation saying that she had previously been told by her gastroenterologist (from another institution) that since the nodule had been stable for two years, there was nothing to be concerned about. The question to be addressed here is: was this correct?

The problem of adrenal incidentaloma has become a recurrent issue for clinicians as increasing numbers of chest and abdominal CT scans are performed. The term "adrenal incidentaloma" is commonly used to refer to nodules greater than 1 centimeter found on imaging, which were unsuspected prior to the study. It also excludes patients known to have active malignancies since these may harbor metastases to the adrenal glands 25-50% of the time. Tumors which are particularly prone to metastasize to the adrenal glands include lung, breast, kidney, and melanoma.[1] The extent of the problem can be estimated from autopsy data, which report the prevalence of adrenal nodules ranging from 2.1% in younger populations less than 30 years of age and increasing to 7-10% in those over 70. The overall incidence of adrenal nodules on CT and MRI ranges from 0.42-4.4% and may be increasing as the technology improves with ever higher resolution scans.

The incidence of adrenal incidentaloma is equal in men and women, is rare in children, increases with age, and appears to be more frequent in whites than blacks. Despite earlier reports based on ultrasound, there appears to be an equal distribution between the right and left sides. Earlier reports of an increased incidence on the right appear to be an artifact of easier visualization of the right adrenal gland on ultrasound.[2] The vast majority of these incidentalomas, approximately 80% of the total, are benign, non-secreting adenomas. Approximately 5-10% are benign, secreting adenomas; 2-5% adrenal cortical carcinoma; about 5% pheochromocytoma; and 1% or less aldosteronoma. The remainder consists of myelipomas, cysts, neural lesions, which include ganglioneuroma and neuroblastoma, hemorrhage, granulomas, amyloid, and when bilateral, the lesions of congenital adrenal hyperplasia, pituitary Cushing's and macronodular adrenal hyperplasia.

The salient issue for clinicians is to determine which lesions need to be removed and which need to be followed, or alternatively the twin questions of which lesions are likely to be malignant and which lesions are likely to be secreting hormones. Multiple authors[3-11] have attempted to address this problem.

Determination of the likelihood of malignancy is usually made on radiological grounds. A homogenous appearance with smooth margins suggests a benign lesion, whereas heterogeneity in appearance and irregular margins raises increased concern. In the past, size was considered the most accurate predictor of malignancy versus benignity. Lesions greater than 6 centimeters in diameter were thought to have an approximately 25% likelihood of malignancy and 1-2% for those in the 4-6 centimeter range. However, there is no absolute separation in size between benign and malignant lesions. It is important to remember that at any cut off, the number of benign lesions will far exceed the number of malignant lesions.[2,8]

Growth is another characteristic, which is assessed in evaluating these lesions over time. It is currently recommended that repeat CT's be performed at 3-6 months for higher suspicion lesions and 6-12 months for lesions which are less suspect, followed by another study at 24 months. Benign pheochromocytomas may grow at approximately 0.5-1 cm per year and adrenal cortical carcinoma at greater than 2 cm per year.[4] While most authors agree that any tumor, which enlarges by more than 1 cm over the observation period, should be removed, there is also a consensus that most adrenal incidentalomas that grow are benign and that there are no data which conclusively identify an optimal follow-up imaging strategy.[3,9,10]

More recently characterization of these lesions by Hounsfield units has been recognized as having better accuracy in separating benign and malignant lesions. Hounsfield units (HU) represent a linear transformation of the attenuation coefficient of the x-ray beam with distilled water being defined as zero and air as -1000 at STP. In general, fat containing lesions will have an HU of <20. Adrenal cortical adenomas usually contain fat and usually are found to have

<20 HU's. However, about 30% of benign adenomas are not lipid rich and will have higher HU's. Pheochromocytomas generally have much higher HU's, almost always over 20, but occasionally between 10 and 20. Most have HU's that are quite a bit higher with 50% more than 110 HU's in one study.[8] Their appearance is also usually vascular and may be hemorrhagic, cystic, or bilateral, so there are other CT hints that a pheochromocytoma may be present. Below 10 HU's, lesions are generally considered benign and if below -30 or -40 are considered benign lipomas for which no further workup is needed. Alternatively, the lipid content of these lesions can be assessed by chemical shift T1-weighted MRI, but that is usually not done because of the greater expense of MRI. However since serial studies are sometimes performed, its advantage is that there is no radiation exposure that can be considerable in serial abdominal CT's.

The remaining radiological criterion by which these lesions are evaluated is contrast washout. Washout refers to the rapidity with which the contrast medium dissipates from the tumor and can be referred to as "absolute," which takes into account the HU's prior to dye administration or "relative" looks only at the decrease following dye administration. An absolute washout of 60% or relative washout of 40% at 15 minutes is highly indicative of benignity.

One should also be aware that other imaging modalities, particularly PET scans, may sometimes be used in evaluating adrenal nodules. PET scans are most useful in looking for metastases. They have some recognized pitfalls including false negatives due to necrosis, hemorrhage, and failure to see small lesions less than 1 centimeter in diameter. Likewise, about 16% of benign adenomas and some benign pheochromocytomas will present as false positives.

Finally, a word must be said about the use of FNA in investigating these lesions. One should be aware that although the cytology from an FNA may distinguish a metastatic from a primary malignancy, it cannot distinguish a cortical adenoma from a cortical carcinoma. Most important, one should never proceed with an FNA until pheochromocytoma has been excluded biochemically.

How was the gastroenterologist's advice about the adrenal incidentaloma? Based on the above discussion, we can see that taking into account the anatomical characteristics of this patient's lesion the gastroenterologist was likely correct in the sense that this patient has a small lesion that has remained stable over time and just misses the criterion of size greater than 4 cm. He was remiss, however, in not considering the second issue of concern, which is whether this lesion could be a functional lesion secreting a hormonally active substance.

With regard to syndromes from hormonally active adrenal incidentaloma, there are really just 3 entities of concern: hyperaldosteronism, pheochromocytoma and the Cushing's spectrum, which includes both traditional Cushing's syndrome and the once controversial but increasingly accepted entity of subclinical Cushing's syndrome.

Since aldosteronomas rarely present as adrenal incidentalomas and since they constitute 1% or less of these lesions, the general consensus is that hyperaldosteronism should be evaluated only in those patients who have either hypertension or hyperkalemia. In addition, one should keep in mind that once a person gets beyond the age of 40, the incidence of essential hypertension increases with aging so that removal of an aldosteronoma, even if present, may not cure the underlying hypertension, and the patient may still need to stay on medical therapy.

Likewise, the evaluation of pheochromocytoma should be restricted to those patients with lesions with greater than 10 HU's. However, since not all pheochromocytomas actively secrete hormones, the presence of hypertension is not a prerequisite to proceed with an evaluation of pheochromocytoma. It is important to identify pheochromocytoma in non-hypertensive patients because such lesions do have the potential to become hormonally active with the devastating consequences of excess catecholamines.

The third entity, which is important to exclude, is Cushing's syndrome. The phenotype of classical Cushing's syndrome includes diabetes, hypertension, hirsutism, striae, depression, amenorrhea, central obesity, moon facies, increased supraclavicular fat pads, and easy bruising. Aside from classical Cushing's syndrome, there has been increasing concern that some patients with incidentalomas may have a syndrome of "subclinical" Cushing's caused by the subtle but autonomous secretion of cortisol. Generally, the classical phenotype is not present.

While the diagnosis of hyperaldosteronism, pheochromocytoma, and traditional Cushing's is beyond the scope of this paper, some attention will be devoted to the newly described and increasingly accepted entity of subclinical Cushing's because the currently accepted thinking is so contradictory and confused. The diagnosis of classical Cushing's syndrome usually requires abnormalities in 2 tests, and there are numerous tests including dexamethasone suppression, midnight serum cortisol, midnight salivary cortisol, and 24-hour urinary free cortisol to choose from. The current thinking is that the initial test in evaluating for subclinical Cushing's must be an overnight 1 mg dexamethasone suppression test. The reasons given for this approach is that since one is looking for only subtle abnormalities in regulation there may not be enough excess cortisol to be recognized in the non-dynamic tests, particularly the urinary-free cortisol. More importantly since one is looking for autonomy of cortisol production by the lesion, only a dynamic suppression test will reveal subtle autonomy, if present. In a normal person, the morning cortisol will be less than 1.8 mcg/dL after taking 1 mg of dexamethasone the night before the test. However, the criterion used for adequate suppression for subclinical Cushing's is 5 mcg/dL. This is necessary since using the usual 1.8 mcg/dL cut off for a normal response would identify too many false positives. Of course, this is another way of saying that the prior probability of disease is so low that the usual criteria for Cushing's have to be suspended. There is also concern that values between 1.8 and 5 mcg/dL may not be clinically relevant. Normally, anyone who suppressed only to levels between 1.8 mcg/dL and 5 mcg/dL would be considered to have Cushing's, if a second confirmatory test was also positive. This is not

considered applicable to patients who do not have overt signs of Cushing's. However, the diagnosis of subclinical Cushing's like that of classical Cushing's requires a second test to be performed. The second test is variously a high morning ACTH, high midnight serum cortisol, an abnormal 24-hour urinary free cortisol, or atrophy of the contralateral adrenal on imaging. DHEA sulfate (which decreases with aging) and midnight salivary cortisol (which produces too many false negatives) are considered unreliable in this context.

The problem with the above approach is that it ends up identifying and labeling some patients who have a 1 mg dexamethasone suppression test greater than 5 mcg/dL and an abnormal 24-hour urinary free cortisol or similar test as "subclinical" Cushing's, whereas they fully meet the biochemical definition for ordinary Cushing's. Furthermore, some[12] have tried to show that these patients have a higher incidence of metabolic abnormalities in patients with adrenal incidentaloma to justify the acceptance of an entity called "subclinical Cushing's". However if a patient has diabetes, hypertension, and obesity, and then is identified with the above biochemical profile, especially if the metabolic abnormalities resolve with removal of the suspect adrenal gland, it is hard to see why they should be labeled as having anything other than traditional Cushing's syndrome.

No one really knows how to follow incidentaloma patients whose initial biochemical profile is normal. Because of observations that hormone abnormalities are identified in follow-up testing but that the new abnormalities occur before 4 years, the current recommendation is that follow-up cortisol tests and possibly tests for catecholamines be done yearly for 4 years.[4] The rate of conversion from normal to subclinical Cushing's varies in different papersbut is likely about 8% over 4-5 years.[1,9] However, others have questioned this approach, suggesting that such repeated follow-up is costly, unlikely to yield new abnormalities, or exposes the patient to unnecessary testing.[11-13]

As for the above patient, she has not had any evaluation of hormonal activity, so an overnight dexamethasone test and a 24-hour urine collection for fractionated metanephrines will be recommended.

As a footnote, it should be remembered that it was the patient's complaint of otherwise undiagnosed abdominal pain that led the gastroenterologist to order the initial CT scan. At her diabetes evaluation, it was noted that she was taking metformin. The metformin was stopped; her abdominal pain resolved. Had this etiology of her abdominal pain been recognized from the first, she probably never would have had the original CT scan, which has led to a repeat radiological study with inevitable x-ray exposure. Now, there is a recommendation for low-yield biochemical testing, which if it places her within the spectrum of "subclinical" Cushing's, could lead to a recommendation for surgery. Even that might be controversial and have a less than certain benefit.

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