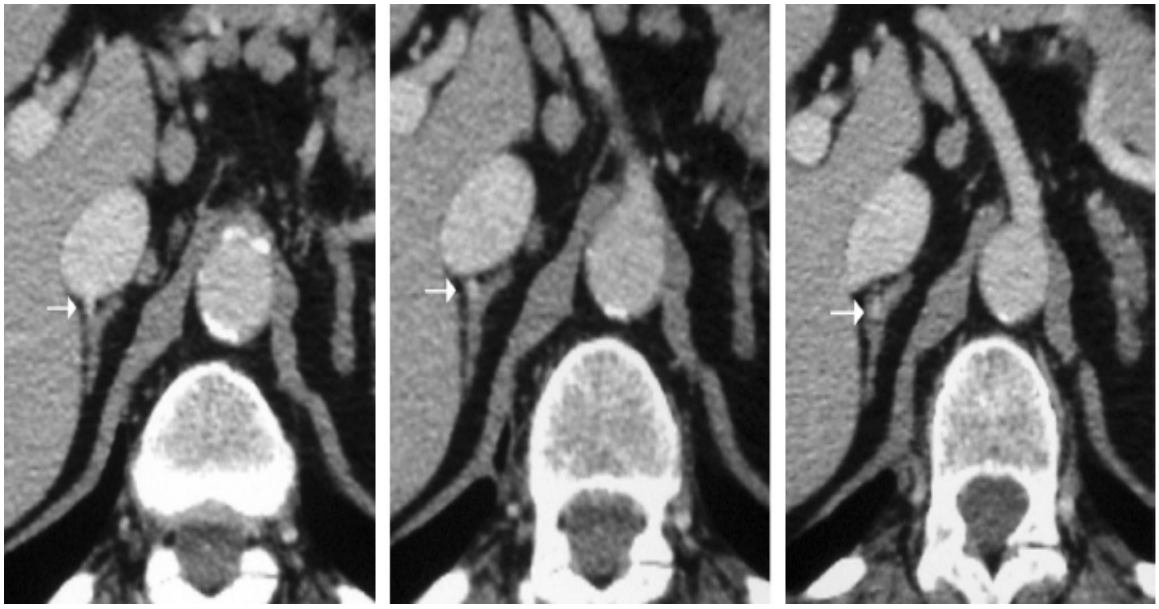
Adrenal Incidentalomas for the Internist



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Purpose and Overview: The purpose of this presentation is to understand how to approach the work-up and evaluation associated with an incidental adrenal nodule. With advances in imaging techniques, adrenal incidentalomas are frequently being discovered. The approach to an adrenal nodule requires a good history and physical examination. In the process, the appropriate differential diagnoses of an adrenal incidentaloma can be considered. However, a majority of the time patients are likely to have adrenal tumors. As such, the basic questions of whether these tumors are functional and malignant need to be addressed. After such an evaluation, the proper referral to endocrine surgery or clinical monitoring can be pursued.

Educational Objectives:

1. Discuss the differential diagnosis of an adrenal incidentaloma
2. Review the diagnostic tests necessary when evaluating an adrenal incidentaloma
3. Understand when to refer a patient for surgical evaluation of an adrenal incidentaloma
4. Highlight new areas of research in the understanding of adrenal tumors

Introduction:

With the advent of advanced imaging modalities such as computerized tomography (CT) scans and magnetic resonance imaging (MRI), more people are being discovered to have incidentalomas from many different organs that may or may not have come to attention otherwise. This phenomenon is becoming of increasing importance to the internist as incidental lesions are found. There becomes an uncertainty as to what requires and what does not require attention. In this review, we will concentrate on the evaluation and management of adrenal incidentalomas.

An adrenal incidentaloma is defined as an adrenal lesion that is discovered by chance when imaging is performed for other reasons (1). The prevalence of adrenal incidentalomas is up to 4% with the use of high resolution CT scans, and incidence increases with age (2). It is estimated that patients younger than 30 years have less than a 1% chance of developing adrenal incidentalomas, whereas those greater than 70 years have an approximately 6.9% chance of having an adrenal incidentaloma (2),(3),(4). From autopsy studies, it appears that both sexes are affected equally (5). However, from CT studies, a higher female prevalence is noted (6),(2).

When evaluating an adrenal incidentaloma, it is important to think about the differential diagnosis of an adrenal mass. The history and physical guides a clinician to think about infectious diseases, cancer history (which may relate with metastatic disease), enzyme deficiencies (such as congenital adrenal hyperplasia), and primary adrenal tumor causing hormone hypersecretion. For example, if there is a history of tuberculosis or histoplasmosis, the adrenal mass may represent an infectious lesion. In the setting of a cancer history, such as melanoma, breast or lung cancer, the likelihood that the adrenal incidentaloma may be due to metastatic disease becomes higher (7). The frequency of malignancy in adrenal incidentalomas varies. In a meta-analysis of large studies which included unselected patients, it was found that there was a low prevalence of primary adrenocortical carcinoma and metastasis (8).

When considering tumorigenic aspects of the adrenal nodule, the clinician needs to ask two basic questions (1):

1. Is the lesion functional?
2. Is the lesion a cancer?

Imaging Phenotype:

When answering the question of whether the adrenal lesion is cancer, it is helpful to look at the computed tomography (CT) imaging phenotype. Evaluating the size of the nodule, x-ray attenuation, pattern of enhancement and de-enhancement of the nodule (contrast wash-out), smoothness of the borders, and nodule homogeneity are helpful characteristics to look at. Specifically, the characteristics for aggressive lesions include nodule size greater than 4 cm, irregular borders, heterogeneous density, delayed contrast wash-out, and increased Hounsfield Units (HU). HU is a semi-quantitative method of measuring x-ray attenuation. A lower HU would be consistent with a higher fat density and a higher likelihood of the nodule being benign. If the HU is less than 10, then the likelihood of the nodule being a benign adenoma is 100%. Not only is a low HU consistent with a benign lesion, but size less than 4 cm, round shape, and homogenous density are other characteristics of benign cortical adrenal tumors. Refer to Figure 1 for an example of a benign cortical adrenal adenoma.

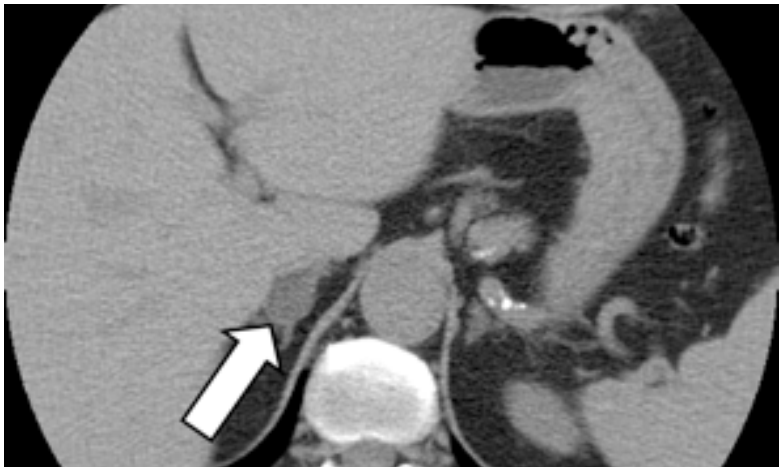


Figure 1: A benign cortical adenoma (shown by the arrow) has features consistent with small size, homogeneous texture, round shape, and regular borders.

Notably, HU is a useful tool, as size alone cannot predict malignancy in these tumors. According to one study, although 25% of adrenal tumors larger than 6 cm turned out to be adrenocortical carcinomas, 2% of adrenocortical carcinomas were less than 4 cm (9). As there tends to be a higher lipid content in benign cortical adenomas, the majority of adrenal adenomas are in a range of -5 to 15 HU (10) (5). However, a higher HU can be seen in benign lipid poor adenomas (10). Additionally, a high HU is seen in adrenocortical carcinomas, pheochromocytomas, and metastatic lesions (11). See Figure 2 for an example of a malignant cortical adrenal tumor.

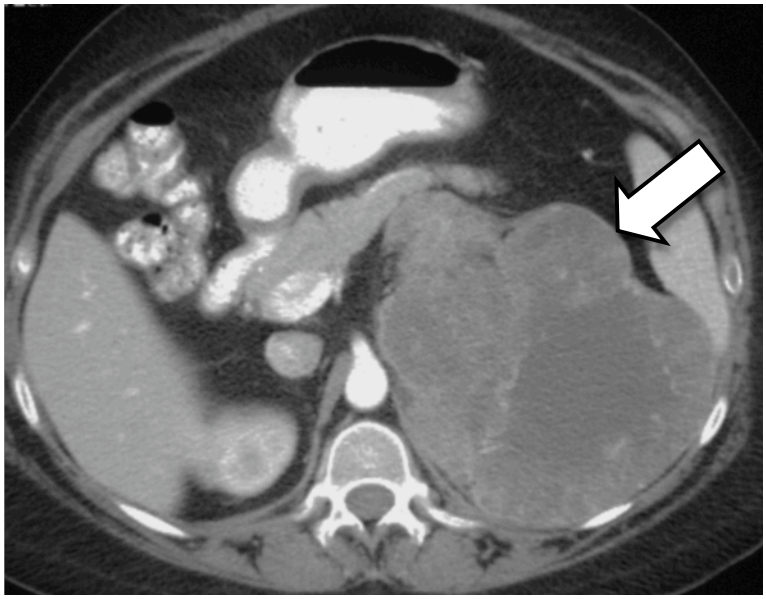


Figure 2: Adrenal cortical carcinoma with characteristics of large size, irregular borders, and heterogeneous texture.

Other than lipid content, contrast wash-out can also be very helpful in determining if the lesion has characteristics of a benign versus malignant process. Benign adenomas demonstrate a wash-out of greater than 60% after a 10-15 minute delay following intravenous contrast administration, whereas metastatic lesions and adrenocortical carcinomas have less than 40% (low) wash-out (4). Other than CT, on MRI evaluations, when lesions are hypodense in relation to the liver on T1 weighted images, they tend to be consistent with a benign lesion (11). Additionally, in cases of metastatic lesions, an 18FDG PET scan can be helpful (12).

Hormonal Evaluation:

All patients that present with an adrenal incidentaloma need a hormonal evaluation. The clinician needs to look for the presence of primary hyperaldosteronism, Subclinical Cushing's Syndrome (SCS), and pheochromocytoma. The following tests to look for hormone function (listed by descending order through the adrenal cortex and into the adrenal medulla, Figure 3) should be considered as an initial screen.

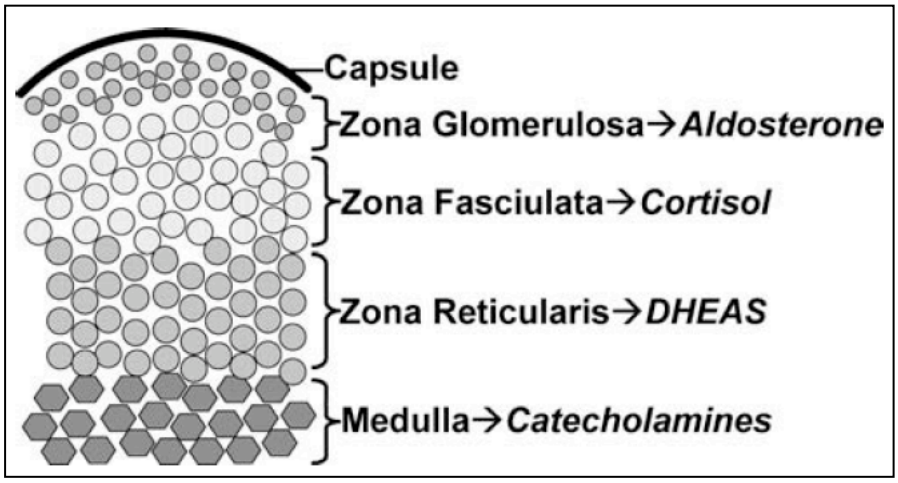


Figure 3: Hormones produced from respected zones of the adrenal gland. Reproduced from Rev Endocr Metab Disord, 2007 (13).

Primary Hyperaldosteronism: plasma aldosterone and renin levels should be drawn in the early morning hours in those patients that have hypertension (14). Note that patients who are on spironolactone, angiotensin converting enzyme inhibitors (ACE-I), or angiotension receptor blockers (ARBs) may have altered aldosterone and renin ratios.

Subclinical Cushing's Syndrome (SCS): 1 mg dexamethasone suppression test. Patients with SCS will not necessarily look Cushingoid but will have an abnormal dexamethasone suppression test (>5 μg/dL) (15).

Pheochromocytoma: plasma metanephrines or 24 hour urine for metanephrines and catecholamines. It is important to note that plasma metanephrines have good sensitivity but lower specificity (16), (17). Certain medications may also interfere with testing, such as tricyclic antidepressants (TCAs), phenoxybenzamine (18), levodopa, and cocaine (19). Additionally, elderly patients with hypertension may have false positive testing with plasma metanephrines. Therefore, ordering a 24 hour urine for catecholamines and metanephrines will be more useful.

Primary Hyperaldosteronism:

Aldosterone producing adenomas (APAs) are adrenal tumors usually less than 2 cm that produce excess aldosterone. Aldosterone is a hormone that is secreted by the zona glomerulosa of the adrenal cortex, and is involved in sodium, potassium, and water balance. It is estimated that 1-2% of patients with adrenal incidentalomas have primary hyperaldosteronism (3). Contrary to popular belief, the majority of patients with APA actually

have normokalemia, however, most will have hypertension. According to one study that evaluated patients with an adrenal incidentaloma, of the 169 patients with hypertension, only 4% had elevated aldosterone to renin activity suggesting hyperaldosteronism. Furthermore, of those patients without hypertension, none of them had hyperaldosteronism (20). Therefore, as per the Endocrine Society recommendations, only those patients with hypertension in addition to adrenal incidentaloma should be evaluated for hyperaldosteronism (14).

Screening tests for hyperaldosteronism include morning aldosterone and plasma renin activity. The ratio of aldosterone to renin activity is then evaluated to determine the possibility of hyperaldosteronism. Many endocrinologists use an aldosterone to renin ratio of at least 20 as their cutoff (21). However, just because the aldosterone to renin ratio may be elevated, this does not always mean the patient has hyperaldosteronism. As a result, aldosterone cut off values for hyperaldosteronism have been studied. A value of an aldosterone level of <10 ng/dL makes it unlikely the patient has hyperaldosteronism (22). Once a screen is positive, it is confirmed with a salt suppression test. It is important that the patient is normokalemic and not on spironolactone, which can interfere with testing. Also, it is not recommended for patients with renal failure or congestive heart failure to receive a salt load for a suppression test. In these patients, it may be more appropriate to repeat the aldosterone and renin levels. Once hyperaldosteronism is confirmed, the patient should undergo an adrenal venous sampling study (AVS). Even though an adrenal nodule is seen, the nodule may be non-functional, and the wrong adrenal could be removed. That is why AVS is recommended especially for those over the age of 40 years (23). Of note, the patient should not undergo an AVS if he/she does not desire surgical intervention and wants to be treated medically.

An exciting new development in the field of hyperaldosteronism involves the discovery of the *KCNJ5* gene (24). Two mutations in the inwardly rectifying potassium channel (*KCNJ5*) selectivity filter were discovered (G151R and G168R). Both mutations increase sodium conductance in the zona glomerulosa cells and causes cell depolarization. This allows opening of calcium channels and aldosterone production as well as cellular proliferation. These mutations were found in 8 of 22 APAs examined in one study (35).

Subclinical Cushing's Syndrome:

First described over 35 years ago, Subclinical Cushing's Syndrome (SCS) is defined as cortisol hypersecretion, however not enough to cause overt Cushing's Syndrome (25). The prevalence of SCS found in patients with adrenal incidentalomas is estimated to be 5% (1).

In SCS, cortisol hypersecretion is enough to suppress ACTH levels and result in an abnormal low dose dexamethasone suppression test. Some of the patients may have a slightly elevated 24 hour urine cortisol, whereas others may have completely normal 24 hour urine cortisol. There has been controversy in how SCS should be diagnosed, as some investigators may look for an abnormal 24 hr urine profile, while others may look for an abnormal dexamethasone suppression test. Despite the controversies, a combination of an abnormal 1 mg dexamethasone suppression test and a low ACTH level are helpful in making the diagnosis (9). Specifically, a cortisol value of greater than 5 μg/dL after a 1 mg dexamethasone suppression test is helpful in diagnosing SCS (26).

After a diagnosis is made, treatment for SCS may involve close monitoring or surgical resection of the responsible adrenal mass. Studies have shown that removal of the adrenal gland causing SCS can result in improvement in blood pressure, diabetes, and lipids (27), (28), (29). The decision to surgically remove an adrenal gland versus to closely monitor is pushed towards surgery if metabolic parameters such as glucose levels, weight, and/or blood pressure readings are becoming worse, and the patient clinically requires an aggressive treatment plan.

Adrenal Cortical Carcinoma (ACC):

ACC is a rare, aggressive tumor whose clinical manifestations cause Cushing's Syndrome nearly 50% of the time (30). The 5-year survival rate is less than 40% (31). Its incidence is 1-2 per million population per year (32). ACC has a bimodal age distribution, affecting either small children or people who are in their 30s or 40s (33).

In the pathogenesis of this tumor, several genes and associated syndromes are implicated, such as the inactivating mutation for the *menin* gene in MEN-1 syndrome (ACC, carcinoid, pituitary, pancreatic, and parathyroid tumors). Another inactivating mutation implicated in ACC includes *p53,* a tumor suppressor gene that causes Li-Fraumeni syndrome (ACC, osteosarcoma, and brain tumors) (34). On the other hand, in Beckwith-Wiedemann syndrome (ACC, neuroblastoma, and Wilm's tumor), there is an activating mutation of the *CTNNB1* gene, which affects the Wnt signaling pathway involved with cellular proliferation (35). A new marker associated with poor overall survival in ACC is Steroidogenic Factor-1 (SF-1), a transcription factor associated with adrenal and gonadal development that has been shown to be elevated in ACC tumors. In one study that looked at 160 ACC samples, only 2% of the tumors were negative for SF-1. Furthermore, high SF-1 did not correlate with good clinical outcome (36).

Patients that develop ACC tend to have rapid development in tumor growth. As a result, in the case of a secreting tumor, clinical manifestations can also develop rapidly. For example, if the tumor secretes glucocorticoids in excess, patients can develop a Cushingoid appearance within 6 months. When evaluating such patients, besides obtaining a history and physical, biochemical evaluation for ACTH, DHEAS, androstenedione, testosterone and 24 hour urine for cortisol should be performed. Radiographic studies include CT scan as well as positive electron tomography (PET) scan. It is not advised to perform FNA of the suspected tumor due to concern for tumor seeding.

Treatment for this disease has been challenging. In 2012, the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma (FIRM-ACT) compared regimens of etoposide, doxorubicin, and cisplatin with mitotane (EDP/M) versus streptozocin with mitotane (Sz/M) (37). EDP/M was found to have a higher response rate compared to Sz/M (23% vs 9%), along with a longer median progression-free survival rate (5 months vs 2 months). However, there was no significant difference in overall survival.

Aldosterone and Cortisol Co-secreting adenoma:

Traditionally, it was well known that ACC tumors secrete all of the hormones produced by the adrenal cortex. However, early stages of ACC or adenomas that make more than one hormone can be missed if a full evaluation of a perceived adrenal adenoma is not completed. Patients with aldosterone and cortisol co-secreting tumors present with hypertension, and may or may not have Cushing's features. It is estimated that 74% of these patients may have subclinical Cushing's (38). Knowing whether or not these patients have cortisol hypersecretion is important, as these patients can develop adrenal crisis if steroids are not given after adrenalectomy (38, 39).

Biochemically, patients with aldosterone and cortisol co-secretion may have an elevated aldosterone to renin ratio, along with an abnormal dexamethasone suppression test, and possibly an elevated 18-hydroxy-cortisol level (38) (40). Radiologically, distinguishing between aldosterone plus cortisol producing adenomas versus aldosterone only producing adenomas (APA) can be done by evaluating the size of the tumor. APAs tend to be slightly larger than 1.0 cm as compared to aldosterone plus cortisol producing tumors which will be over 2.0 cm (39). Figure 4 below shows an aldosterone and cortisol co-secreting tumor.

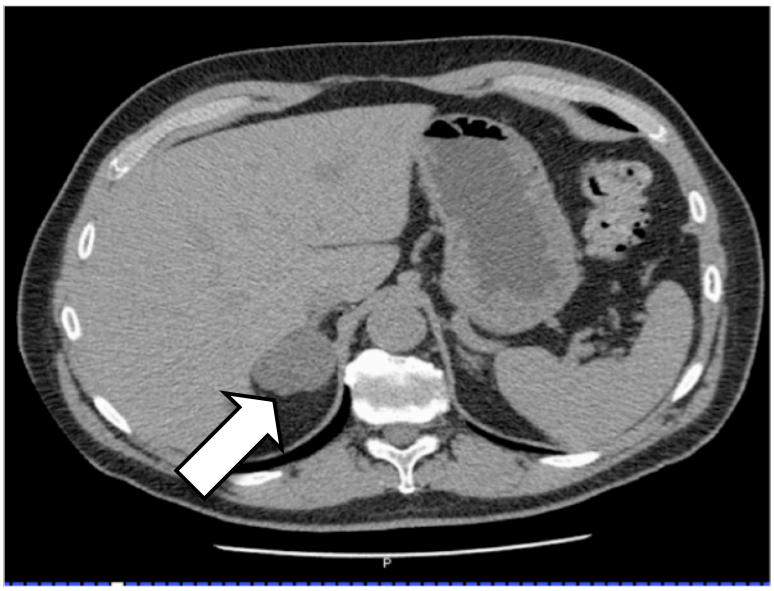
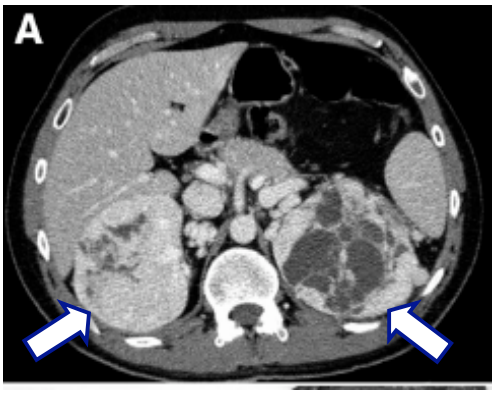


Figure 4: Aldosterone and cortisol co-secreting tumor. These co-secreting adenomas are larger than typical aldosterone secreting tumors, which are usually less than 2 cm.

When these tumors are surgically resected, evidence for malignancy can be investigated by the pathologist using the Weiss criteria. Pathologically, the presence of enzymes for steroidogenesis have been demonstrated whether it is by RT-PCR, immunohistochemistry (IHC), or northern blot (38). However, no exact pattern has been consistent in the current literature. When evaluating patients with possible aldosterone plus cortisol co-secreting tumors, it is important not only to consider intra- and post-operative steroids, but also to determine if the tumor could be a carcinoma. This can be assessed by the presence of metastatic disease as well as by pathological examination.

Adenoma of the Zona Reticularis:

The zona reticularis is the third layer in the adrenal cortex and is involved in making androgen precursors. Such precursors include androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form DHEAS (41). DHEA and DHEAS levels rise in early puberty and reach peak concentrations in early adulthood, followed by a steady decline with age. A case of a patient with bilateral macronodular hyperplasia of the zona reticularis was reported and confirmed by mRNA, protein, and enzymatic activity (42). This is a case of a 29 year old man with a six year history of bilateral maconodular hyperplasia that was incidentally discovered when he was being evaluated for nephrolithiasis (Figure 5).



B HORMONE DATA WITH DYNAMIC TESTING

Measurement	Basal (ULN)	Cosyntropin	Dexamethasone* (* 2 mg/d X 4d)
Cortisol	9 µg/dL	26	0.8
11-deoxysteroids	0.9 µg/dL	2.6	
17-OHP	57 ng/dL	181	
DHEA	17,477 (<1,250 ng/dL)		22,893
DHEA-S	1,645 (<457 µg/dL)		2,036
17-OH Pregnenolone	1,014 (<450 ng/dL)		1,536
Androstenedione	2,177 (<250 ng/dL)		2,681
Testosterone	327 ng/dL		545
Urine free cortisol	10 µg/d		
ACTH	15 pg/mL		

Figure 5: Bilateral adrenal hyperplasia, consistent with a (A) DHEA producing tumor. (B) Biochemical data with dynamic testing consistent with DHEA producing tumor.

The patient did not have cortisol excess, did not complain of hyperandrogenism, and had fathered two children. His testosterone level was normal; however, his DHEA, DHEAS, 17-pregnenolone, and androstenedione levels were markedly elevated. None of these values were suppressed by dexamethasone (Figure 5). The significance of this is that men may not necessarily have apparent clinical manifestations from androgen excess as a result of this type of tumor. Nonetheless, tumor of the zona reticularis should be considered in men with bilateral macronodular hyperplasia. On the other hand, women with an adenoma of the reticularis may have symptoms related to severe androgen excess. Therefore, besides considering Cushing's Syndrome and congenital adrenal hyperplasia in women with androgen excess with abnormal adrenal imaging, tumor of the zona reticularis should be considered.

Pheochromocytoma:

Pheochromocytomas are catecholamine secreting tumors that arise from the adrenal medulla. The prevalence of these tumors in patients that have adrenal incidentalomas is estimated to be 3-4% (8). It is striking to note that prior to 1985, less than 10% of pheochromocytoma cases were incidentally discovered; whereas, from a German chart review, it was found that up to 25% of pheochromocytomas are being discovered incidentally these days (43). Among the patients that were found to have a pheochromocytoma, 12.5% were normotensive (43).

On imaging, pheochromocytomas can be large or small. More often, they tend to be round, have necrotic regions, are possibly cystic (44), and have HU greater than 10 on non-contrast CT imaging (45). There is a debate as to which test is the best screening test for pheochromocytomas. It is agreed that plasma metanephrines are good screening tests as negative results virtually exclude a pheochromocytoma. However, if a patient has a dopamine

secreting tumor, a 24 hour urine collection for metanephrines and catecholamines is helpful (46).

Once a biochemical diagnosis of pheochromocytoma is established after the discovery of the incidentaloma, the patient should be preoperatively managed with an alpha antagonist such as phenoxybenzamine for at least 2 weeks (47). Since phenoxybenzamine may cause orthostatic hypotension, nausea, vomiting, and reflex tachycardia (48), some clinicians prefer to use short acting alpha-1 antagonists such as doxazosin, which can be given at night. Patients with pheochromocytoma should never be started on a ß-blocker before alpha blockade, as there is a risk of cardiovascular collapse due to unopposed alpha-receptors. After adequate alpha blockade, the patient may then be started on ß-blockers to control tachycardia (26). Calcium channel blockers are another option, as these medications help against coronary vasospasm induced by high catecholamines. For patients who have excessive side effects from alpha-receptor antagonists, calcium channel blockers can be given in addition to a low dose alpha-blocker or may be used in substitution. (49). For patients with large, hormonally active pheochromocytomas, some institutions use a tyrosine hydroxylase inhibitor, called alpha-methyl tyrosine (50). However, not all institutions carry this agent. The cornerstone to preoperative management centers on adequate blood pressure and heart rate control, starting with alpha blockade.

Over the last 10 years, great strides have been made in discovering new genes associated with pheochromocytomas. Clues to the pathogenesis of human pheochromocytoma derive from monogenic tumor syndromes, which predispose one to pheochromocytomas. Genes that have been associated with human pheochromocytomas include Neurofibromatosis (*NF-1*), von Hippel-Lindau (*VHL*), Transmembrane 127 (*TMEM127*), MYC associated factor X (*MAX*), and *RET* proto-oncogene (51) (52). Genes associated with extra-adrenal pheochromocytomas (paragangliomas) include five nuclear genes (*SDHA*, *SDHB, SDHC, SDHD, SDHAF2*) that encode subunits of the mitochondrial enzyme succinate dehydrogenase, which catalyzes the conversion of succinate to fumarate in the Krebs Cycle (53). It is thought that these genetic mutations can be divided into two basic categories: hypoxia pathway and cell proliferation pathway. It is well known that mutations that affect succinate dehydrogenase (*SDHx*) genes can induce a pseudohypoxic state. Not only do the *SDHx* genes affect the hypoxia pathway, but the hypoxia induced factor 2 alpha (*HIF2*α) gene, newly discovered to be associated with paraganglioma development, does as well (54). Considering the pathways associated with these genes, new therapeutic modalities are being tested in patients with malignant pheochromocytomas/paragangliomas.

Bilateral Adrenal Adenomas:

The differential diagnoses to consider in patients with bilateral adrenal adenomas include pheochromocytoma (patients with *VHL, MEN2* gene mutations), congenital adrenal hyperplasia (diagnosed by checking morning 17-hydroxyprogesterone followed by cosyntropin stimulation test), cortical adenomas that may cause SCS, metastatic disease, and infectious etiologies such as histoplasmosis as well as tuberculosis.

Fine-Needle Aspiration (FNA) of adrenal nodule:

Patients with adrenal incidentalomas should NOT get an FNA biopsy of the mass until pheochromocytoma is ruled out (55). In addition if there is suspicion that a patient has ACC based off of radiographic and biochemical findings, then a biopsy should not be undertaken due to concern for tumor seeding (56). FNA biopsy of an adrenal mass can be considered in patients who have a history of malignancy such as lung, kidney, melanoma, or breast cancer where metastatic disease may be suspected, but only after a pheochromocytoma has been ruled out (4).

Guidelines:

It is agreed that patients with adrenal incidentalomas need to undergo biochemical testing to evaluate for pheochromocytoma, SCS, and if hypertensive for hyperldosteronism. However, no clear guidelines exist on how often a patient needs to be monitored, both biochemically and radiographically. From a radiographic standpoint, frequent imaging with CT scans can lead to more ionizing radiation, which can lead to a similar risk of developing malignancy as that of the adrenal nodule becoming malignant (8). According to the American Association of Clinical Endocrinologists (AACE) guidelines, for patients with tumors less than 4 cm, follow-up evaluation should take place every 3-6 months, then annually for 1-2 years (4). Tumors greater than 4 cm should be referred for surgical evaluation. Also, tumors that increase in size by 0.8 cm within one year after biochemical testing is completed should be referred for surgical evaluation.

Conclusions:

Patients presenting with an incidentally discovered adrenal mass need a careful history and physical examination. The basic questions that need to be asked are: is the tumor functional

and is it malignant? Biochemical testing is performed to evaluate which hormones the tumor is producing. Plasma metanephrines are good screening tests to determine if a patient has a pheochromocytoma. If there is a higher index of suspicion of a pheochromocytoma, a 24 hour urine for catecholamines and metanephrines should be ordered. Low-dose dexamethasone suppression test is a reasonable test in combination with the clinical presentation to determine if a patient has SCS. If a patient is hypertensive, evaluation of a morning aldosterone and renin are useful to determine the possibility of hyperaldosteronism (Table 1).

Suspected diagnosis	Screening test	Confirmatory test
Pheochromocytoma	Plasma metanephrines	24 hr urine for metanephrines and catecholamines
Subclinical Cushing's	1 mg Dexamethasone suppression test	Low ACTH and DHEAS would help support diagnosis
Hyperaldosteronism	Plasma aldosterone and renin	Oral salt load Saline suppression test

Table 1: Tests needed for evaluation of an adrenal incidentaloma

It is important for a clinician to think about other entities, such as ACC, which is aggressive and needs immediate multidisciplinary attention with an endocrinologist, surgeon, and oncologist. Other entities that can affect clinical management include co-secreting adenomas, such as aldosterone and cortisol. Once these tumors are identified, patients may require steroid supplementation to avoid adrenal crisis post-operatively. For females presenting with hirsutism, consideration of a tumor of the zona reticularis should be entertained, as these patients may have high levels of DHEAS. Besides biochemical testing, radiographic characteristics of the tumor are helpful, especially parameters such as size and attenuation expressed in HU. Size greater than 4 cm is worrisome, as is HU greater than 20. Malignancy,

metastatic disease, and pheochromocytoma tend to be associated with higher HU. Follow-up for adrenal masses for tumors < 3 cm is unclear. However, monitoring patients every 6-12 months for about 2 years is reasonable. See Figure 6 for an algorithm. Perhaps one of the most important principles the internist needs to remember is not to biopsy an adrenal mass unless there is very good evidence that the patient does not have ACC, and pheochromocytoma has been ruled out!

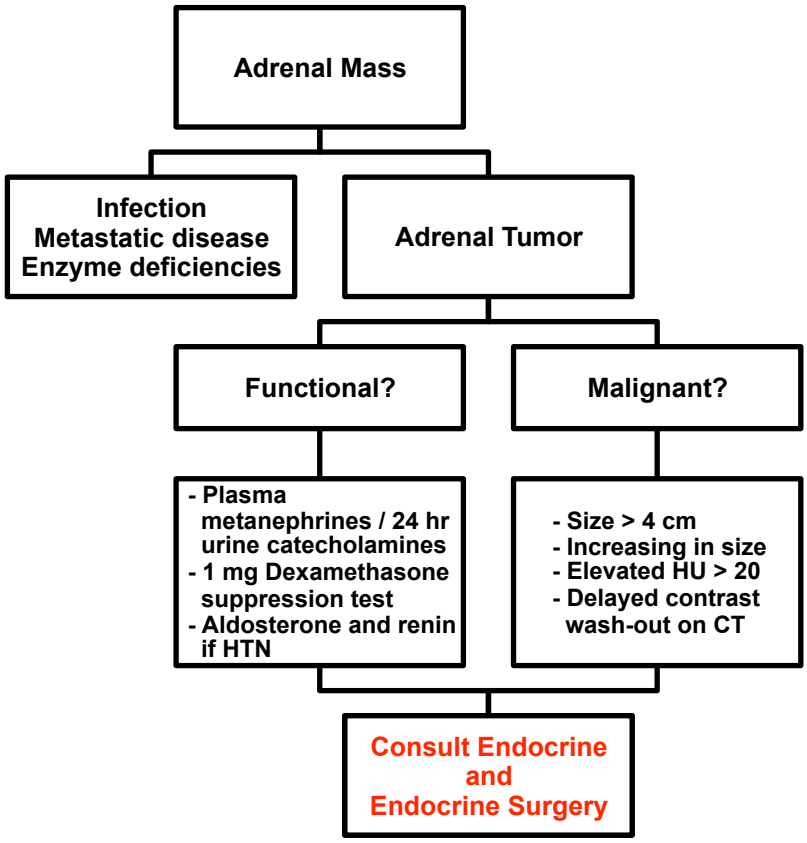


Figure 6: Algorithm for evaluation of an adrenal incidentaloma

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