Adrenal incidentaloma: A puzzle for clinician

Sunil M. Jain

Department of Endocrinology and Diabetology, TOTALL Diabetes Hormone Institute, Indore, Madhya Pradesh, India

ABSTRACT

An adrenal incidentaloma (AI) is a puzzle for clinician. In the era of widespread use of CT and MRI, it is becoming an increasingly frequent diagnosis. A detailed list of investigations is ordered to diagnose pathology responsible for AI. Most likely etiology of AI is pathology of AI is benign non-functional adenoma. But looking to the need of specific preoperative preparation for functional adrenal adenoma and importance of early diagnosis in adrenal carcinoma, a complete workup is essential. CT scan of adrenals with contrast gives maximum information about nature of lesion. In general, a lesion more than 6cm or a functioning AI or tumor signal intensity of more than 10HU on unenhanced image, significant enhancement on contrast and deenhancement in signal intensity of less than 50% is suggestive of carcinoma and must be removed. Those AI which are left for observation, also needs regular testing and if found functional on subsequent follow-up or if their size enlarge, they must be removed.

Key words: Adrenal carcinoma, adrenal incidentaloma, incidentally found adrenal lesion

INTRODUCTION

An adrenal incidentaloma (AI) is defined as an adrenal lesion that is discovered on a radiologic study done for some other purpose. Adrenal incidentaloma is an “umbrella” term that covers much of pathologies sharing the same way of incidental discovery. In the era of widespread use of CT and magnetic resonance imaging (MRI), AI is becoming an increasingly frequent diagnosis. Further, when a diagnosis of AI is made, there are lot many concerns in mind of patient and family, primarily due to possibility of malignancy. This warrants a detailed investigation plan to diagnosis pathology responsible for AI.

The prevalence of adrenal incidentalomas based on reports summarizing the result of 25 autopsy studies is about 6%.[1-3] The mean prevalence of adrenal incidentalomas using high-resolution computed tomography (CT) scans is about 4%.[4,5] As the age advances, prevalence of adrenal incidentalomas increases. AI is reported in less than 1% in patients younger than 30 years and up to 7% in patients over age of 70 years.[2,3,6]

CAUSES OF ADRENAL INCIDENTALOMA

Pathology of AI may vary from simple benign cyst or lipoma to adrenal carcinoma. The differential diagnosis of the adrenal mass comprises a long list like adenoma, myelolipoma, cyst, lipoma, pheochromocytoma, adrenal cancer, metastatic cancer, hyperplasia and tuberculosis.[7]

Below mentioned table shows etiology of AI

The prevalence of some of the common underlying etiologies in patients with adrenal incidentaloma [Table 1].[8]

In general, there are 80% chances that AI will be a simple nonfunctioning adenoma, 10% chances are for functional adenoma most likely Cushing or pheochromocytoma, 2-3% will have adrenocortical carcinoma/metastatic lesion while remaining 6-7% AI will belong ganglioneuromas, myelolipomas or benign cysts.
OBJECTIVE OF INVESTIGATING AI

When AI diagnosis is made, clinicians need to find answer for two questions:
1. Is the lesion functional?
2. What is the nature of the lesion - benign or malignant?

Looking to these 2 objectives, all patients with an adrenal incidentaloma should be evaluated for possibility of hyperfunctioning lesion of adrenal cortex i.e., Cushing’s syndrome/hyperaldosteronism and adrenal medulla i.e., pheochromocytoma. If the AI is nonfunctional then all attempts are to be done to find nature of the tumor.

CLINICAL APPROACH AND WORK UP IN CASE OF AI

Any patient having AI should be worked up for functional status of tumor and its nature. For this objective, clinician should obtain relevant history to exclude possibility of functional tumor. History of weight gain or development of centripetal obesity, easy bruisability, severe hypertension, diabetes, virilization, proximal muscle weakness, fatigue, osteoporosis etc., are suggestive of Cushing syndrome. If patient informs about sudden or severe headaches, weight loss, anxiety attacks, sweating, cardiac arrhythmias, or palpitations etc., then possibility of pheochromocytoma is likely. While presence of hypertension, fluid retention or a history of hypokalemia suggests hyperaldosteronism. History should include information about risk factors for malignancy as well as recent weight loss. Common lesions which can metastasize to adrenal are carcinomas of the lung, breast, kidney and gastrointestinal tract and melanoma or lymphoma (Lau et al., 2002). Generally adrenal metastases are typically bilateral and larger than 3cm but rarely, they may be unilateral and small.

Physical examination should include blood pressure and pulse and to look for physical signs of cortisol excess like central obesity, striae, muscle wasting, hirsutism or other signs of virilization.

INVESTIGATIONS IN A CASE OF AI

Endocrine tests

- Dexamethasone suppression test
- ACTH (adrenocorticotropic hormone) levels
- Plasma free metanephrine and normetanephrine levels
- 24 h total urinary metanephrines
- Ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA)

If cortisol level is more than 5.0µg/dL on 1mg overnight dexamethasone suppression test, this is suggestive of Cushing syndrome. If no clinical features of Cushing syndrome are present but cortisol levels are more than 5 on 1 mg overnight dexamethasone suppression test then this entity are known as sub-clinical Cushing syndrome or SCS. Presence of low ACTH further supports clinical or sub-clinical Cushing syndrome. Two day low-dose dexamethasone suppression test may also be needed to establish the diagnosis of CS or SCS.

Elevated plasma free metanephrine and normetanephrine levels and 24h total urinary metanephrines suggest the presence of pheochromocytoma. In patients with pheochromocytoma, hypertension may or may not be present. Radiology findings are very important clue to diagnosis. As a general rule, normal plasma metanephrine rules out a diagnosis of pheochromocytoma. Patients with elevated plasma metanephrines within three to four times, the upper limit of normal should undergo measurement of 24 h urine metanephrines.[10,11]

Patients with hypertension who have a ratio of plasma aldosterone concentration (PAC) (ng/dL) to plasma renin activity (PRA) (ng/mL per hour) of >20 while not taking spironolactone and mineralocorticoid receptor blockers is suggestive of primary aldosteronism. In addition to ratio, serum aldosterone level below 0.25 nmol/liter (9ng/dl) makes a diagnosis of primary aldosteronism highly unlikely.[12,13] Measurement of plasma aldosterone to renin ratio (ARR) is the best initial test for the evaluation of primary aldosteronism.[14-16]

For measurement of ARR it is better if it is done after correcting hypokalemia, while the patient is on salt restriction and in the morning in a sitting position after resting for at least 15 min.

In most patients, a combination of 1-mg overnight dexamethasone suppression test (ONDST), plasma
metanephrines along with aldosterone and plasma renin activity (PRA) measurements is in morning hour during sitting position, is a good initial screening plan to decide functional status of AI.

**Radiologic imaging**
The primary goal of imaging is to distinguish among adrenal adenoma, adrenal carcinoma, pheochromocytoma and metastatic lesions. The diagnosis of an adenoma relies on the presence of intracellular lipid in the adrenal lesion, which can be identified by CT or MRI. Generally MRI does not offer any advantage over CT except in case of pheochromocytoma which has very characteristic MRI image.

**CT scan**
If a protocol is followed for CT scan then many conclusions can be drawn. Adrenal protocol for CT scan includes unenhanced images and then images obtained 1 min after IV injection of contrast media to see enhancement and then imaging after a 10 to 15 min delay to look for de-enhancement.

Clinician should look for signal intensity of the lesion, which is expressed in Hounsfield units. HU of noncontrast image, then percentage enhancement in signal intensity at 1 minute post contrast and percentage deenhancement of signal intensity at 10 to 15 min should be studied.

A benign lesion generally has signal intensity of less than 10 HU on unenhanced image, while it has deenhancement in signal intensity of more than 40 to 60% in 10 or 15 min. Benign adrenal lesions will commonly enhance up to 80 to 90HU and wash out more than 50% on the delayed scan, whereas Adrenal carcinoma/metastatic tumors and pheochromocytomas will show washout of less than 50% (8 [EL 2]). Caoli et al.,[17] characterized 127 adrenal masses and reported the criteria for benign lesions as less than 10 HU on unenhanced CT scan and absolute percentage enhancement washout of at least 60% was 98% sensitive and 92% specific.

On non-contrast CT, some benign adrenal lesions do not have attenuation values of less than 10 HU and may have values of 20 to 40HU. This result is found in lipid poor adenomas. In these cases, a washout of >50% will often allow the diagnosis of an adenoma to be made.

Pheochromocytomas behave differently on CT scan. Pheochromocytomas have signal intensity of more than 100HU on non-contrast CT, while on contrast pheochromocytoma enhance and don’t deenhance by more than 40-60% like other benign lesions so on CT these lesions behave like adrenal CA.

**MRI**
The accuracy of MRI to the differentiation between benign and malignant tumors is comparable to that of CT scan. Usually, malignant masses are hypointense on T1-weighted images and hyperintense on T2-weighted images, with strong enhancement after contrast injection and delayed washout.

MRI may be helpful in the diagnosis of pheochromocytoma, where it can provide better information than CT scan. High signal intensity on T2-weighted MRI is characteristic of pheochromocytoma.

**Fine-needle aspiration**
This test has very few indications for work up of AI. Image-guided fine-needle aspiration (FNA) can be done in suspected cases of metastasis with no primary visible or in a suspected case of Adrenal CA where pheochromocytoma has been ruled out.

**Other tests**
Include metaiodobenzylguanidine (MIBG) and 131I-iodocholesterol (NP-59) scintigraphy, adrenal vein sampling and many other biochemical tests which can be ordered for suspicion of specific diagnosis.

**MANAGEMENT OF ADRENAL INCIDENTALOMA**
AI will need surgery or observation. All functional lesions, all malignant lesions as well as all suspicious lesions must be removed. If the clinical findings and work-up suggest a functional lesion then lesion specific preoperative and postoperative management is required.

Following is AACE guidelines for decision making in a case of AI [Figure 1]:

---

**Figure 1: AACE guidelines for decision making in a case of Adrenal Incidentaloma**

---
AI NEEDING SURGERY

The risk of malignancy increases significantly with tumor size greater than 4 cm and therefore, many organizations recommend removal of all adrenal incidentalomas more than 4 cm in size that lack characteristic benign radiological features. But if size is more than 4 cm and lesion is clearly benign on radiologically like a 5 cm homogenous AI with non-contrast signal intensity or attenuation value of less than 10 HU is close to 0%.

Lack of change in the size of an adrenal mass has also been proposed as an indicator of the benign nature of an adrenal tumor. In a recent study by Pantalone et al., reporting on 75 surgically resected adrenal masses with at least two imaging studies 3 to 12 m apart, a change in tumor size of 0.8 cm provided the highest combined sensitivity (60%) and specificity (84.6%) for the differentiation of a benign vs. a malignant adrenal mass.

AI NEEDING OBSERVATION

If AI is non-functional, size is less than 4 cm and has benign characteristics on imaging then it can be kept under observation. Benign CT characteristic is meant by attenuation value or signal intensity of less than 10 HU, homogenous appearance, enhancement on contrast and deenhancement by more than 60%. Even if size is more than 4 cm but less than 6 cm and has benign characteristics then also it can be kept in observation.

During observation period, functional assessment and radiology has to be repeated. In general, no repeat testing is needed in hyperaldosteronism. While for pheochromocytoma and Cushing syndrome, annual biochemical screening is suggested. Although the cost-effectiveness of this strategy is unknown, most authors recommend annual biochemical screening for catecholamine and cortisol excess for 4 year.

Patients with AI in observation should have a repeat CT study in 3 to 6 m and then yearly for 2 years. If lesion grow at least 0.8 cm over 3- to 12-month follow-up then surgical excision should be considered.

SUMMARY

As the name suggests, AI is incidentally detected. Objective of detailed investigations for this incidentally detected finding is to decide which AI needs surgery. For this objective, clinician has to first decide whether AI is functional or non-functional. In general, all functioning AI has to be surgically removed. If AI is non-functional, and if risk of probability of malignancy is high then it must be removed. Size of AI and its radiologic characteristics can guide about malignant potential. Non functional AI with size of more than 6 cm needs removal. AI less than 4 cm, looking benign on imaging can be left for observation while AI of 4 to 6 cm size management is a area of uncertainty. If such AI noticed clearly benign by imaging criterion, then can be left for observation. Those AI which are left for observation, must undergo periodic testing and if there is increase in size or if it becomes functional then AI should be removed. Thus with the help of endocrine tests and CT scan, a vigilant clinician can take appropriate decision for the management of AI.

REFERENCES

1. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 2007;356:601-10.
2. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: Update in diagnosis and management. Endocr Rev 2004;25:309-40.
3. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. Endocr Rev 1995;16:460-84.
4. Barzon L, Sonino N, Fallo F, Palu G, Boscaro M. Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol 2003;149:273-85.
5. Bovio S, Cataldi A, Reimondo G, Sperone P, Novello S, Bernuti A, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. J Endocrinol Invest 2006;29:298-302.
6. Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am 2000;29:159-85.
7. Cook DM. Adrenal mass. Endocrinol Metab Clin North Am 1997;26:829-52.
8. Zeiger MA, Siegelman SS, Hammerian AH. Medical and surgical evaluation and treatment of adrenal incidentalomas. J Clin Endocrinol Metab 2011;96:2004-15.
9. Lau J, Balk E, Rothberg M, Ioannidid JP, DeVine D, Chew P, et al. Management of clinically inapparent adrenal mass. Evid Rep Technol Assess (Summ) 2002;56:1-5.
10. Hemmelgarn BR, McAlister FA, Groover S, Myers MG, McKay DW, Bolli P, et al. The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension. Part I-blood pressure measurement, diagnosis and assessment of risk. Can J Cardiol 2006;22:573-81.
11. Anagnostis P, Karagiannis A, Tzimalos K, Kakafika AI, Athyros VG, Mikhailidis DP. Adrenal incidentaloma: A diagnostic challenge. Hormones (Athens) 2009;8:163-84.
12. Mosso L, Carvajal C, González A, Barraza A, Avila F, Montero J, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003;42:161-5.
13. Stowasser M, Gordon RD. Primary aldosteronism-careful investigation is essential and rewarding. Mol Cell Endocrinol 2004;217:33-9.
14. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93:3266-81.
15. McKenzie TJ, Lillegard JB, Young Jr WF, Thompson GB. Aldosteronomas-state of the art. Surg Clin North Am 2009;89:1241-53.
16. Hiramatsu K, Yamada T, Yukimura Y, Komiya I, Ishihara K, et al. A screening test to identify aldosterone-producing...
Jain: Adrenal incidentaloma

adenoma by measuring plasma renin activity. Results in hypertensive patients. Arch Intern Med 1981;141:1589-93.

17. Cailli EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR, et al. Adrenal masses: Characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629-33.

18. Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez G, Bogabathina H, Levin HS, et al. Clinical utility of noncontrast computed tomography attenuation value (Hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab 2005;90:871-7.

19. van Erkel AR, van Gils AP, Lequin M, Kruitwagen C, Bloem JL, Falke TH. CT and MR distinction of adenomas and nonadenomas of the adrenal gland. J Comput Assist Tomogr 1994;18:432-8.

20. Lee MJ, Hahn PF, Papanicolaou N, Egglin TK, Saini S, Mueller PR, et al. Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology 1991;179:415-8.

21. Singer AA, Obuchowski NA, Einstein DM, Paushter DM. Metastasis or adenoma? Computed tomographic evaluation of the adrenal mass. Cleve Clin J Med 1994;61:200-5.

22. Miyake H, Takaki H, Matsumoto S, Yoshida S, Maeda T, Mori H. Adrenal nonhyper functioning adenoma and nonadenoma: CT attenuation value as discriminative index. Abdom Imaging 1995;20:559-62.

23. McNicholas MM, Lee MJ, Mayo-Smith WW, Hahn PF, Boland GW, Mueller PR. An imaging algorithm for the differential diagnosis of adrenal adenomas and metastases. AJR Am J Roentgenol 1995;165:1453-9.

24. Korobkin M, Brodeur FJ, Yutzy GG, Francis IR, Quint LE, Dunnick NR, et al. Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. AJR Am J Roentgenol 1996;166:531-6.

25. Macart M, Rofsky NM, Nadich DP, Megibow AJ. Non-small cell lung carcinoma: Usefulness of unenhanced helical CT of the adrenal glands in an unmonitored environment. Radiology 1998;209:807-12.

26. Boland GW, Lee MJ, Gazelle GS, Halpern EF, McNicholas MM, Mueller PR. Characterization of adrenal masses using unenhanced CT. An analysis of the CT literature. AJR Am J Roentgenol 1998;171:201-4.

27. Nwariaku FE, Champine J, Kim LT, Burkey S, O’keefe G, Snyder 3rd WH. Radiologic characterization of adrenal masses: The role of computed tomography-derived attenuation values. Surgery 2001;130:1068-71.

28. Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA, et al. Management of the clinically inapparent adrenal mass (“incidentaloma”). Ann Intern Med 2003;138:424-9.

29. Schteingart DE. Management approaches to adrenal incidentalomas. A view from Ann Arbor, Michigan. Endocrinol Metab Clin North Am 2000;29:127-39.

30. Pantalone KM, Gopan T, Remer EM, Faiman C, Ioachimescu AG, Levin HS, et al. Change in adrenal mass size as a predictor of a malignant tumor. Endocr Pract 2010;16:577-87.

Cite this article as: Jain SM. Adrenal incidentaloma: A puzzle for clinician. Indian J Endocr Metab 2013;17:S59-63.

Source of Support: Nil, Conflict of Interest: None declared.