Case discussion in Medicine

Adrenal Incidentaloma — Case based approach

Ravi Kant[1], Mukesh Kumar Bairwa[2], Mahendra Kumar Meena[3], Monika Pathania[4]

Adrenal incidentaloma is reported between 2-6% in radio-imaging, the lesions may be inactive or might secrete homones like glucocorticoid, mineralo-corticoid, sex steroid or at times catecholamines. The size of lesion is a determinant of nature of lesion, the larger ones are usually malignant, there is lot of gray area over the size of the lesion to classify as malignant but usually a lesion greater than 4 cm is taken a malignant. Radio-imaging by CT/MRI is a good initial investigation for characterization of lesion as adenoma vs non-adenomatous. Functional evaluation by radio-nucleide scan can differentiate between various sub-types.

[*J Indian Med Assoc* 2020; **118(9):** 53-6]

Key words **: Adrenal, incidentaloma, glucorticoid, mineralocorticoid, adenoma.**

Adrenal Incidentaloma is a common radiological accompaniment, its work up, diagnosis and management poses potential challenges and is quite confusing. The current case based approach will definitely aid in the evaluation of adrenal incidentaloma.

Case Report

A 68 -year-old lady presented with complaints of acute onset haematuria. It was insidious in onset, painlessdark coloured, moderate amount, with no history of loin/ abdominal pain and urinary symptoms like dysuria, polyuria, intermittency and hesitancy. She was evaluated for the above symptoms by a physician and a couple of investigations were advised along with abdominal ultrasound . Abdominal ultrasound showed a right adrenal mass measuring 3cm with no other abnormality detected and Endocrinology consult was sought for further evaluation of the adrenal mass with haematuria.

Q1. How to proceed for further history and examination ?

History of present illness : On further enquiry about the other symptom complex, she denied any history of excessive weight gain, central obesity, easy bruising, purplish stria, generalised weakness or paroxysmal muscular weakness, increased hair growth over body, recent onset of hypertension and /or glucose intolerance-ie, features suggestive of **glucocorticoid excess.**

She gave no history of paroxysms of headache, excessive sweating, palpitations suggestive of catecholamine secreting adrenal tumour like **pheochromocytoma.**

She had her menopause at the age of 50 years and denied any history of excessive facial hair growth, skin changes like acne, deepening of voice, clitoromegaly, male pattern baldness – features suggestive of **androgen secreting adrenal tumour**;

Also there is no history of vaginal bleeding and breast tenderness – features suggestive of **oestrogen secreting adrenal tumours**. She also deniedany history of easy fatigability and weight loss.

There was no family history of any intrabdominal mass; paroxysmal symptoms of hypertension, palpitations, headache; haematuria; renal tumours; excessive weight gain with increased hair growth over body/face. There is no history of anorexia, nausea, vomiting and weight loss

Past history : In past she suffered from transient ischemic attack 3 years before and recovered completely.

She underwent excision of malignant melanoma at upper back 5 years before. There is no other chronic illness like hypertension, diabetes mellitus or chronic infections like tuberculosis.

Family history : None of her family members suffered from adrenal tumour or melanoma

Drug history : She was currently on Clopidogrel for an episode of TIA

Editor's Comment :

- Adrenal incidentaloma is being more commonly diagnosed due to better radio-imaging, its clinical suspicion requires meticulous work up and treatment.

Department of Medicine, All India Institute of Medical Science Rishikesh, Uttarakhand 249203
[1]MD (Med), Additional Professor and Head and Corresponding Author
[2]MD (Med), Assistant Professor
[3]MBBS, Junior Resident (Medicine)
[4]MD (Med), Associate Professor

Received on : 13/08/2020
Accepted on : 19/08/2020

Examination —

The general survey revealed hyperpigmentation of skin at the upper back at the excision site of malignant melanoma. She was moderately built and nourished. She had a weight of 160 pounds with a height 5 feet 10 inches metre and BMI : 23kg/m^2, HR- 76/min, supine BP-144/76 mmHg and standing was 138/80 mmHg.

She had no features of Cushing's syndrome – facial plethora, wide violaceous striae on abdomen,thighs or other places, no cuticular atrophy, bruises or proximal myopathy. Her Ferriman- Gallwey scoring was 8/30 and had no features of virilization. There was no acne, temporal recession of hair, low pitched voice, and clitoromegaly.

Systemic examination was normal with nolocal abdominal tenderness/ renal angle tenderness and no palpable abdominal mass.

By history and physical examination, it is more likely that patient has adrenal incidentaloma. Though she lacks the usual stigmata of overt Cushing's syndrome, Subclinical Cushing's syndrome is the commoner presentation amongst the symptomatic adrenal incidentaloma cases followed by Pheochromocytoma and Primary aldosteronism.

Q2. What are probable differential diagnosis?

Differential diagnosis :

1. Adrenal adenoma (Lipid rich)
2. Lipid poor adrenal adenoma
3. Pheochromocytoma
4. Sub clinical autonomous cortisol hypersecretion (Subclinical Cushing's syndrome)
5. Cushing's syndrome
6. Conn's syndrome
7. Carcinoma
8. Metastases
9. Hemangioma
10. Adrenal deposits
11. Ganglioneuroma
12. Tuberculosis
13. Adrenal cyst
14. Myelolipoma

Q3. How to plan further investigations to arrive to narrow diagnosis.

Investigations :

All patients with adrenal incidentaloma should be evaluated for hormonal hyperfunction, 85% are however non-functional[1]. It is important to rule out pheochromocytoma as it can lead to hemodynamic instability even in asymptomatic patients, more so at the time of surgery[2]. Following tests are to be done in cases of adrenal incidentaloma.

A. Biochemical assessments, Electrolytes and Arterial Blood gas analysis : Serum potassium levels vary with aldosterone level, a higher aldosterone level is associated with hypokalemia and metabolic alkalosis whereas a low aldosterone is associated with hyperkalemia and metabolic acidosis.

B. Specific tests for assessing adrenal gland functioning

1. Catecholamines and Metanephrine assessment : Twenty-four hours urinary free catecholamines or metanephrines is a good screening test to rule out pheochromocytoma. It is proven that plasma free metanephrines estimation is diagnostically superior to urinary catecholamines and/or metanephrines, but it's use in diagnosis is limited due to its non-availability at many centers.[3] Currently the diagnostic utility of plasma catecholamines and metanephrines lie in cases where the urinary levels of these compounds are normal and the clinical suspicion of pheochromocytoma is high.

2. Primary aldosteronomas : Primary aldosteronomas (PA) are found in 1.5-3.3% in adrenal incidentaloma. Screening is recommended for hypertensive patients.[4] Almost 40% of patients with PA have normal serum levels of potassium and hypokalemia is not a reliable sign to investigate PA.[5]The diagnostic armamentarium for Conn's syndrome as suggested by Barts is as given in Table 1.

3. Cortisol estimation: There is increasing evidence that there is abnormality in hypothalamo-pituitary-adrenal axis in patients with adrenal incidentaloma even in otherwise non-cushing's patients, better known as sub-clinical autonomous

Table 1 — *Depicting the diagnostic criteria for conn's syndrome*

Conn's: case confirmation			
Confirmatory test	Procedure	Interpretation	Points of note
Oral sodium loading test	200 mmol (6g)/d for 3d Maintain normal K+-24 hr urinary aldo d3-4	PA unlikely if aldo excretion <10µg/dl (27.7nmol) PA likely if >12 mg/d (33.3nmol)	Avoid in cardiac/ renalfailure; uncontrolled hypertn
Sodium infusion test	Infuse 2L saline over 4 hrs Patient recumbent - Samples for K+, cortisol, aldo and renin at 0 and 4 hrs	<5 ng/dl PA unlikely; >10ng/dl PA likely; 5-10ng/dl indeterminate	Avoid in cardiac/ renal failure; uncontrolled hypertn
Fludrosupprn test	FC 0.1mg 6 hrly for 4d Keep K+ normal NaCl – generous PRA and aldo at 1000H on d4 Cortisol at 0700 and 1000H	Upright aldo on d4 >6ng/ml confirms PAPRA must be <1ng/ml/hrCortisol at 1000 should be <0700	May req inpatient stay Good discrimn in large groups of pts.

glucocorticoid hypersecretion (SAGH).The frequency of occurrence of this disorder varies between 1 and 29% depending on criteria used for its diagnosis.[6] Basal serum cortisol estimation at 9:00 AM is the screening test to rule out cushing's syndrome.Various tests for assessment of SAGH are 24 hours urinary free cortisol, midnight plasma cortisol, ACTH and high dose dexamethasone suppression test. However overnight 1 mg dexamethasone suppression test yields a diagnostic accuracy of 98% sensitivity and 80-98% specificity as per NIH consensus statement.[7] Plasma value of >138 nmol/l is associated with significant glucocorticoid autonomy. This should ofcourse be supplemented with one more diagnostic test for assessing hypercortisolism.

4. Androgen levels assessment: It is not a usual diagnostic work up for adrenal incidentaloma. Androgen overproduction is a hallmark of adrenal carcinomas, a low level of dehydroepiandrosterone sulfate is suggestive of adrenal adenoma.

Investigations

CT Scan: The CT scan of this patient is suggestive of an adrenal lesion of 3.4X2.4 cm. This lesion falls in the indeterminate category. The size is a determinant of malignant potential of an adrenal lesion.A lesion more than 3 cm carries a fairly high chances of being malignant.Most of the non-functional adrenal adenoma has an attenuation value less than 10 HU (Fig 1) with a specificity of 98%. [8] This patient has a value 24 HU which of course goes against lipid rich adrenal adenoma.There is still the possibility of lipid poor adrenal adenoma or pheochromocytoma. In any case be it a lipid rich or lipid poor adenoma the absolute wash out must be more than 60% which is not the case here. There is likelihood of pheochromocytoma which is supported by a CT finding of >10 HU and its characteristic of early enhancement and delayed washout. It is definitely going in favor of non-adenomatous lesions as well like adrenocortical carcinoma (ACCs), but most of the ACC are larger than 6 cm and has extension to surrounding structures and heterogenous appearance on CT. The possibility of non-adenomatous lesion is further reinforced by a wash out of only by 19% and early enhancement.Adenoma has an early enhancement and early washout >60% absolute and >40% relative washout. Other possibilities like myelolipoma, cyst, hemangioma, is less likely in view of CT finding having a HU >10 and a cyst does not enhance on contrast, and the wash out characteristics of rest of the lesions. The liver cyst is a benign one and spinal degenerative changes do not contribute to the adrenal lesion.

Plasma levels of catecholamines: Normal 24 hours catecholamine levels reduces the possibility of pheochromocytoma. Serum levels of catecholamines however is a better choice to rule out the diagnosis of pheochromocytoma. Pheochromocytoma may exist even when the catecholamine levels are normal.

Serum Cortisol: Basal Serum cortisol is falling within normal range, this principally rules out a endogenous hypercortisolism, however there can be possibility of sub-clinical autonomous glucocorticoidhy persecretion, this entity is devoid of clinical manifestations of Cushing's but has a higher value of cortisol. To rule out this particular entity there is hardly an agreement on the levels of serum cortisol and

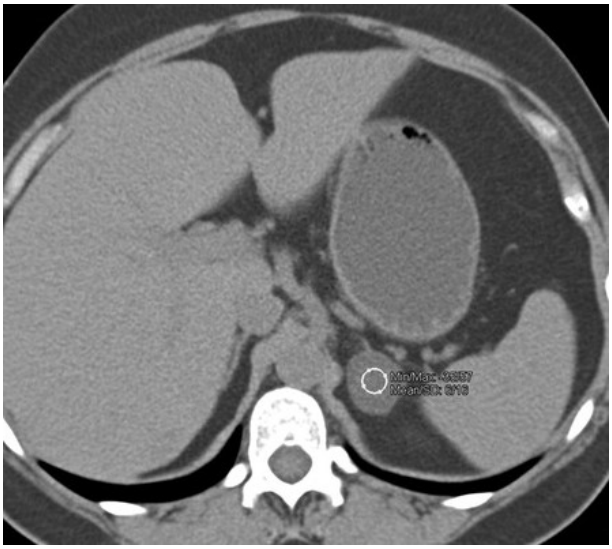


Fig 1 — Left adrenal mass with <10 HU attenuation consistent with non-functional adenoma. [Representative image only, not related to case]

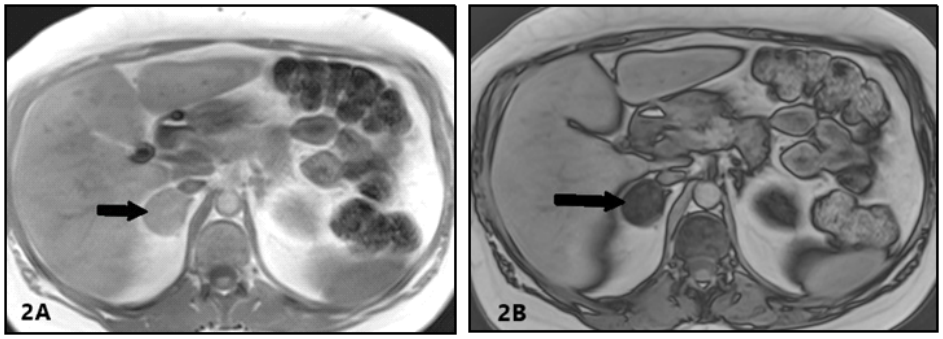
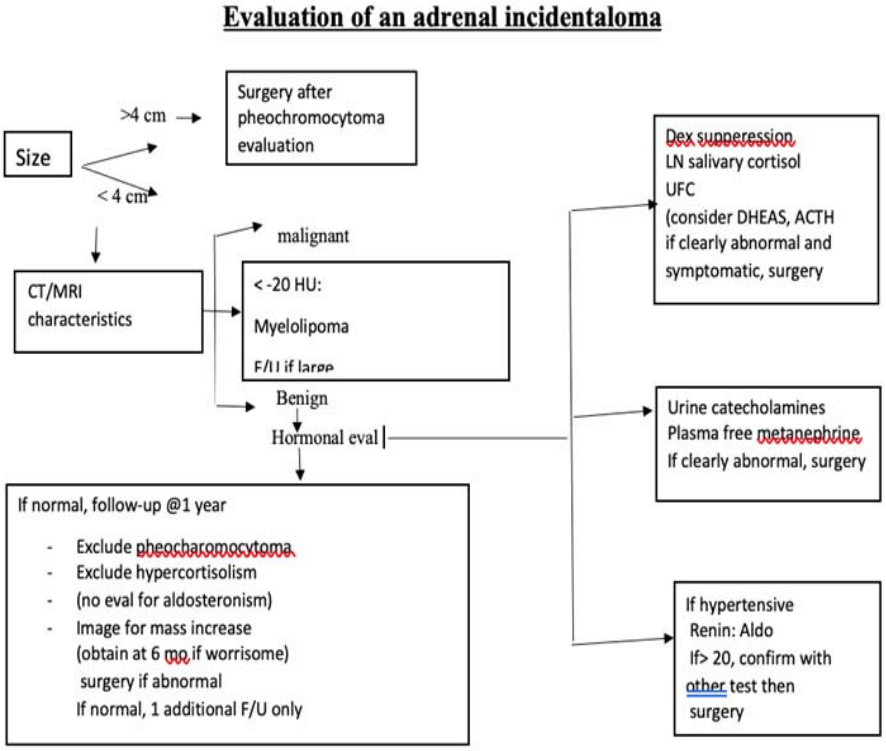


Fig 2 — MRI depicting loss of signal intensity in out of phase image (2B compared to 2A) owing to intracellular fat (Representative image only)

dexamethasone suppression test. The national institute of health has recommended 1 mg dexamethasone overnight test with conventional cutoff of 140 nmol/l.[9] However dexamethasone suppression test using 2 mg dexamethasone 6 hourly for 48 hours is used to exclude Cushing's especially in morbid obesity, alcoholism and diabetes mellitus.[10]Serum cortisol values as low as 50 nmol/l has been used to define sub clinical autonomous cortisol hypersecretion for both Cushing's syndrome and incidentaloma screening.[11] This patient has a 9 AM cortisol of 354 nmol/l and that suppressed adequately to low dose dexamethasone suppression test (LDDST) with a value of serum cortisol of 36nmol/l. The normal response to LDDST suggest a normal response and rules out the possibility of sub clinical autonomous cortisol hypersecretion.

Suggested evaluation of an incidentally found adrenal mass. Surgery for large masses with cause that requires resection, e.g. tuberculosis. LN, Late-night; Aldo, aldosterone; Dex, dexamethasone; F/U, follow-up; eval, evaluation; mo, months.



Q4. After Investigations how to relist the differential diagnosis ?

Relisting of Differential diagnosis: Will like to consider following Differential diagnosis.

1. Pheochromocytoma
2. Carcinoma
3. Metastatic lesion

Q5. What other investigations will help arriving at a diagnosis

Magnetic Resonance Imaging(MRI): MRI with chemical shift imaging (CSI) is the mainstay of evaluation of solid adrenal lesions. It utilizes the differential distribution of protons in fat and water as signals, the CSI signal loss can be measured quantitatively and qualitatively as well (Fig 2). The quantitative assessment is done as adrenal to spleen chemical shift ratio, by dividing the lesion to signal intensity ratios on the in-phaseimages (IP) by the out of phase images (OOP)[12]A. CSI ratio of less than 0.71 at 1.5 T field indicates a lipid rich adenoma. Alternatively adrenal signal intensity index is calculated as (IP-OOP signal intensity)/IP signal intensity X 100%, a measurement of greater than 16.5% at 1.5 T is consistent with a lipid rich adenoma. The sensitivity and specificity of CSI for differentiation of adrenal incidentaloma are reported at 81% to 100% and 94% to 100% respectively.[13] It is noteworthy that adrenal cortical carcinoma and pheochromocytoma demonstrate signal loss on OOP images.[14] ACC are generally heterogenous with areas of high signal intensity on T1 weighted and T2 weighted sequences. As the ACC arises from adrenal cortex hence it contains intracytoplasmic lipids and at times it is difficult to differentiate between adenoma and carcinoma especially when it is small .But otherwise differentiation can easily be done by a large size , heterogenous nature and spread to surrounding structures.