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Adrenal Incidentaloma: A Brief Review

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1. Abstract

Incidentally detected adrenal lesions when radiographic evaluation is done for other reasons are considered as adrenal incidentalomas and the size criteria is more than 1cm. The evaluation and treatment of adrenal incidentalomas are based on the available retrospective evidences as there is lack of prospective randomized trials. Conservative treatment with follow up imaging can be offered to elderly patients with adrenal incidentaloma but young patients needs a careful and prompt attention. We have reviewed the literature of adrenal incidentaloma and tried to concise it in brief. The prevalence of adrenal incidentaloma is higher in elderly, obese, diabetic, and hypertensive patients. Bilateral adrenal masses had been detected in 10-15 % cases. In bilateral masses, there is possibility of one mass will be a non-functional cortical adenoma and the other will be a hormone secreting mass. Functional status of the adrenal lesion alters the treatment plan. Hence, biochemical evaluation is the essential step after radiographic study. Laparoscopic adrenalectomy has similar oncological outcomes as compared to open approach in expert hands.

2. Background

Adrenal incidentalomas are the adrenal lesions with size more than 1cm in diameter and which may be discovered incidentally when Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI) is done for other reasons [1]. Majority of adrenal lesions are asymptomatic, however they are picked up due to advances in radiographic imagings such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). The prevalence of adrenal incidentaloma is higher in elderly patients (10%), obese, diabetic, and hypertensive patients [2]. The prevalence of adrenal incidentaloma is reported around 0.4 % in studies where abdominal CT scans were performed and in other series it is reported as 4.4% where high resolution scanners were used [3, 4]. Bilateral adrenal masses had been detected in 10-15 % cases, reported by two large studies [5, 6]. In bilateral masses, there is possibility of one mass will be a non-functional cortical adenoma and the other will be a hormone secreting mass [6]. Different conditions where these bilateral adrenal lesions can be seen are congenital adrenal hyperplasia, Bilateral Macronodular Adrenal Hyperplasia (BMAH), cortical adenomas, lymphoma, corticotropin (ACTH)-dependent Cushing's syndrome, pheochromocytoma, primary aldosteronism, amyloidosis, infiltrative diseases of the adrenal gland and metastatic disease. Whenever an adrenal lesion is detected, the next question is to rule out its specific characteristics like whether it is malignant or benign and functional or non-functional cortical adenoma [7].

3. Incidentaloma Work Up

Radiographic imaging is the cornerstone in evaluating the nature of adrenal masses. The specific characteristic of adrenal lesions on radiographic imaging helps in determining whether its benign or malignant lesion. The size of the lesion on imaging decides its nature and helps in planning the treatment [8]. The frequency of primary adrenal carcinoma in patients with adrenal incidentaloma is approximately 2 – 5 % and non-adrenal metastases to the adrenal gland accounts about 0.7 - 2.5 % [9].

3.1. Size

The size of the adrenal lesion is an important factor as the maximum diameter of the lesion is predictive of malignancy. The smaller the size of the adrenocortical carcionoma, the better the overall prognosis. It had been postulated by a retrospective series of 62 patients where five-year survival was higher in patients with smaller tumors [10]. The National Italian Study Group reported a 4cm cutoff for the size [11]. However, the size criteria should not be the only parameter which decides the treatment plan. One of the largest retrospective series of 4085 patients with adrenal tumors had shown that leson with size > 4cm was associated with other entities like adrenocortical adenoma, pheochromocytoma and other benign tumors [12]. Multivariate analysis of the study was found to be statistically significant predictors of malignancy with variables like larger tumor size, male sex, older age at diagnosis, higher unenhanced Computed Tomography (CT) attenuation and non-incidental mode of discovery.

3.2. Radiographic Evaluation

Computed Tomography (CT) is the recommended primary adrenal imaging procedure in most cases. The intracytoplasmic fat in adenomas results in low attenuation on unenhanced CT and non-adenomas have higher attenuation in unenhanced CT. A retrospective series of 151 patients with adrenal masses who underwent both a noncontrast CT scan and adrenalectomy had interpreted that a homogeneous adrenal mass with a smooth border and an attenuation value <10 HU on unenhanced CT is very likely to be a benign adenoma [13]. In another retrospective cohort of 353 patients where adrenal lesions were evaluated with CT, concluded that adrenal lesions with unenhanced CT attenuation >10 HU were diagnosed with malignancy with a sensitivity of 100 % and specificity of 33 % [14]. On delayed contrast-enhanced CT, adenomas show rapid contrast medium washout, whereas non-adenomas have delayed contrast material washout [13]. In case of adenoma, after ten minutes of contrast administration, there will be an absolute contrast medium washout of more than 50 %. The role of Magnetic Resonance Imaging (MRI) comes in follow-up imaging to avoid the radiation exposure of repeated CT imaging. On gadolinium Diethylene Triamine Pentaacetic Acid (DTPA)-enhanced MRI, adenomas demonstrate mild enhancement and a rapid washout of contrast, while malignant lesions show rapid and marked enhancement and a slower washout pattern. MR with Chemical Shift Imaging (CSI) accurately distinguishes adrenal adenomas from nonadenomas and it is based on their elevated amounts of intracytoplasmic fat [15] (Table 1).

Table 1: Radiographic features of different adrenal lesions are as follows.

Benign Adenomas [16]	Round and homogeneous density with smooth contour
	Diameter < 4 cm
	Unilateral location
	Low unenhanced CT attenuation values (≤10 HU)
	Chemical shift evidence of lipid on MRI
	Rapid contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of more than 50 %)
Adrenocortical Carcinoma [17,18]	Irregular shape
	Diameter usually >4 cm
	Unilateral location
	High unenhanced CT attenuation values (>20 HU)
	Inhomogeneous density (central areas of low attenuation due to tumor necrosis)
	Inhomogeneous enhancement on CT with intravenous contrast
	Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 %)
	High standardized uptake value (SUV) on FDG-PET-CT study
	Evidence of local invasion or metastases
Pheochromocytoma [19]	Variable size and may be bilateral
	Increased attenuation on unenhanced CT (>20 HU)
	Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 percent)
	High signal intensity on T2-weighted MRI
Adrenal Metastasis [20,21]	Irregular shape and inhomogeneous nature
	May be bilateral
	High unenhanced CT attenuation values (>20 HU)
	Delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 %)
	Enhancement with intravenous contrast on CT
	Elevated SUV on FDG-PET scan

3.3. Tissue Diagnosis

Image guided Fine Needle Aspiration Biospy (FNAB) is a safe procedure with lower rates of complications (around 2.8%). The complications include adrenal and liver hematoma, pneumothorax, pancreatitis, abdominal pain, hematuria, adrenal abscess formation, and tumor recurrence along the needle track [22]. Cytology cannot distinguish a benign adrenal lesion from the adrenocortical carcinoma. It can distinguish between an adrenal tumor

and a metastatic tumor [23]. Pheochromocytoma should always be ruled out with biochemical testing before FNAB as there are chances of haemorrhage and hypertensive crisis with FNAB [24]. Adrenal lesion biopsy is not indicated if the patient has widespread metastatic disease and it is not useful in the routine evaluation of incidentalomas [25, 26].

3.4. Functional Status

Functional adrenal tumors are hyperfuctioning adrenal lesions and there are three conditions where adrenal hyperfunctioning should be considered in patients with an adrenal incidentaloma.

1. Pheochromocytoma
2. Primary aldosteronism
3. Subclinical cushing's syndrome

Most of the times, pheochromocytomas are diagnosed in presymtomatic stage due to widespread use of computed imaging and rest are diagnosed after evaluation of pheochromocytoma-related symptoms [27]. If the unenhanced CT attenuation is ≥10 HU, pheochromocytoma should be evaluated with biochemical testing (but not if it is <10 HU). Small pheochromocytomas (<1.5 cm) may have normal biochemical testing and it has to achieve a critical size to become biochemically detectable. Surgical resection is the choice of treatment for functioning or non-functioning pheochromocytomas.

Primary aldosteronism should be considered if the patient is hypertensive or has hypokalemia. All patients with hypertension and an adrenal incidentaloma should be evaluated by measurements of plasma aldosterone concentration and plasma renin activity. Normotensive patients with spontaneous hypokalemia should also be considered for testing for primary aldosteronism.

Subclinical cushing's syndrome is a cortisol secretion without clinical manifestations of Cushing's syndrome and its detection is more common with adrenal incidentaloma. In case of unilateral adrenal adenoma or bilateral macronodular adrenal hyperplasia, aberrant hormone receptors control the cortisol secretion [28]. These patients do not have typical clinical features of overt cushing's syndrome, however, they may present with osteoporosis, atherosclerosis, dyslipidemia, hypertension, diabetes mellitus and weight gain [29-31]. It is diagnosed with 1 mg overnight Dexamethasone Suppression Test (DST) [32]. Baseline serum Dehydroepiandrosterone Sulfate (DHEAS) level should be estimated before DST. A low DHEAS represents chronic suppression of ACTH secretion. A Clinically significant glucocorticoid secretory autonomy is diagnosed and confirmed by a post-overnight 8 mg DST with 8 AM serum cortisol concentration >1.8 mcg/dL (>50 nmol/L). Some centers are using a higher dose of dexamethasone (3 mg instead of the standard 1 mg) to reduce false-positive results [33]. If the patient is diagnosed as a pheochromocytoma clinically or on the basis of radiographic evaluation, DST should not be performed as there are chances of catecholaminergic crisis. When there is scenario of bilateral adrenal masses which are consistent with solitary bilateral adenomas on cross-sectional computed imaging, consideration should be given to adrenal venous sampling [34].

4. Management

Management of Unilateral Adrenal Lesions:

4.1. Pheochromocytoma

Patients who are diagnosed as pheochromocytoma clinically, biochemically or on the basis of radiographic evaluation should be offered surgical excision of the lesion (Adrenalectomy) as untreated case may lead to significant cardiovascular complications.

4.2. Adrenocortical Carcinoma

Patients with documented evidence of adrenocortical carcinoma or any lesion suspicious for carcinoma should be offered surgical excision of the lesion (Adrenalectomy) as their disease may progress rapidly .

4.3. Aldosteronoma

To avoid and cure aldosterone excess, surgery is the treatment of choice.

4.5. Subclinical Cushing's Syndrome

It is still unclear that which patients with subclinical cushing's syndrome should undergo surgery as there is lack of prospective randomized trials. Younger patients with autonomous glucocorticoid secretion with well-documented glucocorticoid secretory autonomy should be considered for adrenalectomy and if adrenalectomy is planned, perioperative glucocorticoid coverage should be administered as there is a risk of adrenal insufficiency, hemodynamic crisis, and death. Post adrenalectomy in patients with subclinical cushing's syndrome, there may be improvement in certain conditions like improvement in hypertension, glycemic control, weight loss and normalization of markers of bone turnover [35].

4.6. Suspicious Adrenal Lesion

Adrenal lesion with suspicious picture on imaging or size >4cm in diameter should be offered surgery as substantial fraction will be adrenocortical carcinomas. The decision should be taken depending on the clinical scenario, patient's age and functional status of the tumor. Wait and watch policy with follow up imaging may be offered to elderly patients however, young adults with suspicious lesion needs prompt attention.

4.7. Adrenal Myelolipoma

Large amounts of macroscopic fat in an adrenal lesion is diagnostic of a myelolipoma on computed imaging.

It is a benign tumor composed of mature fat with interspersed hematopoietic elements which resembles bone marrow. These are indolent tumors and may grow over time, hence observation with follow up imaging is an option without surgical excision. However, if size > 6cm in diameter or mass-effect symptoms, surgical excision should be considered [36].

5. Management of Bilateral Adrenal Lesions

The decision of surgical excision in the scenario of bilateral adrenal lesions depends upon the degree of cortisol secretory autonomy. Hence, patients with Bilateral Macronodular Adrenal Hyperplasia (BMAH) and clinical Cushing's syndrome usually are best offered with bilateral adrenalectomy, whereas patients with BMAH and subclinical Cushing's syndrome can be addressed with removal of the larger adrenal gland.

6. Conclusion

Benign adrenal lesions can be differentiated with the help of CT and MRI while malignant and metastatic lesions can be identified by 18FDG-PET/CT. Excess of cortisol, metanephrine and aldosterone secretion indicates hyperfunctional state of the adrenal gland. Suspicious adrenal lesions on radiological imaging, persistently enlarging adrenal lesions which are kept on close follow up and adrenal tumors with overt clinical syndromes, should be addressed with surgical resection.

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