Original Article

Presentation and Outcome of Patients with an Adrenal Mass: A Retrospective Observational Study

Abstract

Background: Adrenal masses are uncommon, often present with a wide spectrum of manifestations, ranging from silent, benign incidentaloma to functional and rarely highly malignant neoplasm. The study aimed to evaluate the characteristics and outcomes of patients with an adrenal mass. **Materials and Methods:** This was a single-center, retrospective, observational study on 42 patients diagnosed with an adrenal mass, between August 2010 and August 2019 at our institute. They were studied for clinical, laboratory, radiological, and surgical outcome. All the patients were subjected to computed tomography adrenal protocol and hormonal evaluation (overnight 1 mg dexamethasone suppression test [ONDST] and urinary metanephrine/normetanephrine in all; plasma aldosterone/renin activity ratio [ARR] in patients with hypertension/hypokalemia). **Results:** The mean age of the study sample was 45.2 ± 12.4 years, with female (69%) predominance. Symptomatic adrenal mass (52.4%) was the most common presentation. Abdominal pain (61.9%) and hypertension (54.8%) were the most common presenting symptoms. Obesity and dyslipidemia were present in half of the patients and hyperglycemia in 23.8%. The majority of tumors were benign (90.5%). Most of the adrenals lesions were nonfunctional (47.6%), followed by pheochromocytoma (26.2%), primary hyperaldosteronism (7.1%), and adrenal Cushing's syndrome (7.1%). Most of the lesions were large, i.e., >4 cm (42.8%). The surgical cure was achieved in 74.1% of patients, with good outcome in nonfunctional adrenal adenoma and myelolipoma. Age ≤40 years was associated with functional adrenal mass. **Conclusions:** A higher proportion of patients have functional tumors, with pheochromocytomas comprising 26.3%. Majority of patients achieved surgical cure. Age ≤40 years predicted functionality of adrenal mass.

Keywords: *Adrenal mass, myelolipoma, nonfunctional adrenal adenoma, pheochromocytoma, primary hyperaldosteronism*

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Introduction

The adrenal gland is composed of cortex and medulla, and both have different embryonic origin. The adrenal tumors vary in manifestation, depending on the zone from which they arise from the adrenal gland. The term adrenal mass is not a single entity; instead, it is an "umbrella" definition, comprising a spectrum of various pathological entities.[1] An adrenal mass is incidentally found in up to 4%–7% of patients imaged for nonadrenal disease,[2] with nearly 80% of these masses found to be benign.[3-6] An adrenal incidentaloma is a adrenal mass, which is unexpectedly detected through an imaging procedure performed for reasons unrelated to adrenal dysfunction.[7] This definition excludes patients undergoing imaging procedure as part of malignancy staging and workup. Incidentalomas are uncommon in patients younger than 30 years of age, but increase in frequency with age. The diagnosis of adrenal mass focuses on two main questions: whether the lesion is malignant and or hormonally active.[8]

Almost 15% of patients with adrenal masses present with signs and symptoms of adrenal hormonal excess.[9] Most incidentalomas are adrenocortical adenomas, but occasionally, they represent myelolipomas, hamartomas, or granulomatous infiltrations of the adrenal gland. Functioning tumors include pheochromocytomas and primary hyperaldosteronism, are diagnosed in 11%–15% and 4%–10% of patients with adrenal incidentalomas, respectively, and adrenocortical carcinomas (ACCs) account for around 11% of patients with adrenal incidentalomas.[6,9] Advances in the diagnostic evaluation and utilization

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of minimally invasive surgery have improved the management of adrenal tumors. Pertinent assessment of an adrenal mass is an essential step before its definitive treatment. Radiological evaluation includes computed tomography (CT) with attenuation values expressed in Hounsfield units. The three most essential imaging criteria to distinguish between benign and malignant adrenal lesions are (1) size of the lesion, (2) the CT attenuation value on an unenhanced CT scan, and (3) the percentage of contrast washout. All patients have to undergo hormonal evaluation for subclinical Cushing's syndrome (SCS) and pheochromocytoma, and those with hypertension also require evaluation for primary hyperaldosteronism. Further hormonal evaluation is based on clinical and radiological findings.[10] SCS occurs in up to 20%–30% of all cases.[2]

Functional or malignant adrenal masses require immediate management[11,12] and surgical excision is the treatment of choice for these tumors.[10,13] Laparoscopic adrenalectomy is the treatment of choice, compared with open adrenalectomy. Adequate preparation and close endocrine supervision perioperatively and postoperatively are required for functional tumors.[8] The surgical cure varies with etiology of adrenal mass and is poor in functional and malignant lesions.

Although there are several studies on the characteristics of adrenal mass from centres around the world as well as India.[6,14-19] but to date, there are no reports of the clinical presentation and outcome of patients with adrenal mass from our centre. To date, there are no reports of the clinical presentation and outcome of patients with an adrenal mass from our center. This study was undertaken to determine the characteristics and outcome of adrenal mass in patients who attended and were managed at tertiary care hospital in North India.

Materials and Methods

Subjects

This was a retrospective review of consecutive patients with adrenal lesions discovered via CT scan at a tertiary care hospital between August 2010 and August 2019. The study center is a public tertiary referral teaching hospital with a total bed capacity of almost 850. The study included all patients aged 18 years or older with adrenal mass except patients having adrenal metastases and missing baseline characteristics or incomplete hormonal evaluation. After applying these exclusion criteria, the total number of subjects eligible for the study was 42 (13 males and 29 females). The institutional ethical committee approved the study.

Data collection

Clinical information on all patients with an adrenal mass was retrieved from the hospital records. For each patient, information at presentation and postsurgery was recorded. These included demographic details; clinical presentation; associated comorbidities; physical examination; biochemical, radiological, and hormonal evaluation; and surgical findings. Other routine biochemical and hematological tests (plasma glucose, renal function, lipid profile, serum calcium, full blood count, and electrolytes) were also available.

Adrenal protocol CT scan

For newly discovered adrenal lesion, an adrenal protocol CT was used. This consists of unenhanced images, images obtained 1 min after interneurons injection of contrast media, and imaging after a 10–15-min delay. Criteria for benign lesions include HU of <10 HU on unenhanced CT scan, and absolute percentage enhancement washout of >60%, which has 98% sensitivity and 92% specificity.[20]

Biochemical analysis

The hormonal evaluation included 8:00 am fasting basal serum cortisol level, overnight 1 mg dexamethasone suppression test (ONDST), 24-h urine vanillylmandelic acid (VMA), 24-h urine metanephrine and normetanephrine levels, serum aldosterone level, and plasma renin activity. Autonomous cortisol secretion was excluded when ONDST cortisol levels fell below 1.8 μg/dL, as recommended by the National Institutes of Health.[3] Patients were considered to have SCS if ONDST cortisol level remained above 5.0 μg/dL without features of Cushing's syndrome.[9] When hypercortisolemia was found, confirmatory tests were performed, such as cortisol rhythm, low-dose dexamethasone suppression test (Liddle I test, dexamethasone 0.5 mg p.o. every 6 h for 2 days), urinary free cortisol (UFC), adrenocorticotropic hormone (ACTH) level, and high-dose dexamethasone suppression test (HDDST). The biochemical criteria used for the diagnosis of pheochromocytoma were a 24-h urine fractionated metanephrine level >3 times the upper limit of the normal reference range for the laboratory.[21] Plasma aldosterone/renin activity ratio (ARR) was the screening used for primary hyperaldosteronism, and patients with ARR >20 were suspected of having primary hyperaldosteronism; a saline infusion test was performed to confirm this diagnosis. We grouped all adrenal masses into various diagnostic categories, based on clinical, biochemical, and radiological characteristics.

Diagnosis

Nonfunctional adrenal adenoma was diagnosed when CT scan revealed round-to-oval, homogeneous mass with smooth margins, precontrast <10 HU, >50% washout, ONDST <5 μg/dL, and metanephrines negative.

Pheochromocytoma was diagnosed when CT scan revealed round-to-oval, inhomogeneous adrenal mass, precontrast >10 HU, <50% washout, and urinary metanephrine/VMA ≥3 times the upper limit of normal.

Hyperaldosteronism was diagnosed when the patient presented with hypertension, hypokalemia, ARR >20, positive saline load test, CT features of adrenal adenoma, or hyperplasia.

Adrenal Cushing's syndrome was diagnosed when the patient presented with specific clinical features, ONSDT ≥1.8 μg/dL, LDSST ≥1.8 μg/dL, UFC > upper normal limit (40–120 mg/24 h), 9 am ACTH <10, HDDST <50% suppression, and with CT features of adrenal adenoma.

Myelolipoma was diagnosed when CT scan revealed round-to-oval, homogeneous mass with smooth margins, precontrast <−30 HU, ONDST <5 μg/dL, and metanephrines negative.

ACC was diagnosed when CT scan revealed an irregular and inhomogeneous mass, precontrast >10 HU, <50% washout, and dehydroepiandrosterone sulfate > 800 ug/dL.

Definition

Obesity was defined as body mass index (BMI) ≥25 kg/m^2; hypertension was defined as systolic blood pressure of ≥140 or diastolic blood pressure of ≥90 mmHg or on antihypertensive drugs; diabetes when blood glucose fasting was ≥126 mg/dl or glycated hemoglobin (HbA1c) ≥6.5% or on antidiabetic drugs; and dyslipidemia when triglycerides ≥150 mg/dl, low-density lipoprotein ≥140 mg/dl, or high-density lipoprotein <40 mg/dl in males and <50 mg/dl in females or on statin therapy.

Adrenalectomy was recommended in patients with overt hormonal hypersecretion, a significantly large (diameter >4 cm) or growing mass, or radiographic features suspicious of malignancy. The cure was defined biochemically in secretory tumors as the normal range of hormone, in whom the preoperative levels were elevated and by the absence of tumor on radiological imaging postsurgery. In patients with nonsecretory (nonfunctional) tumors, the cure was determined radiologically by the absence of tumor on radiological imaging postsurgery. Follow-up was undertaken by the endocrinology clinic for all patients and included clinical examination, repeat hormonal testing, and imaging.

Statistical analysis

Descriptive statistics were used for demographic and clinical data. Frequency distribution was assessed in terms of means ± standard deviation for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared using the Chi-square test and/or Fisher's exact test where appropriate. For continuous variables, the independent Student's *t*-test was used. $P < 0.05$ was considered statistically significant. All variables that resulted in $P < 0.05$ in univariate analyses were entered into a logistic regression analysis to assess independent associations between risk factors and functional adrenal tumors. All the analyses were performed using the statistical software known as Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

Results

Demographic data

The mean age at presentation was 45.2 ± 12.4 years (range, 18–62 years). Females (69%) outnumbered the males. Twenty-three patients presented at an age between 50 and 60 years. In all patients, the diagnosis of adrenal mass was made antemortem [Table 1].

Clinical presentation

Table 1 shows the clinical features at presentation. The incidental mode of presentation was noted in 47.6% of patients, whereas others had a symptomatic presentation. The most common symptom was pain abdomen (61.9%). Other symptoms noted were headache, palpitation, hirsutism, and acute abdomen. Abdominal mass was

Table 1: Baseline characteristics of patients with an adrenal mass

Characteristic	Number of patients (%)
Demographic	
Age in years	45.2±12.4 (18-62)
Females	29 (69)
Postmenopausal	13 (44.8)
BMI	24.4±4.7
Mode of presentation	
Symptomatic	22 (52.4)
Incidental	20 (47.6)
Symptoms and clinical findings	
Abdominal pain	26 (61.9)
Headache	11 (26.2)
Proximal myopathy	4 (9.5)
Striae	2 (4.8)
Hirsutism	4 (9.5)
Acute abdomen	3 (7.1)
Palpitation	6 (14.3)
Hypertension	23 (54.8)
Orthostatic hypotension	4 (9.5)
Hyperglycemia	10 (23.8)
IFG	5 (50)
Diabetes	5 (50)
Obesity	25 (59.5)
Dyslipidemia	20 (47.6)
Abdominal mass	8 (19)
Tumor type	
Benign	38 (90.5)
Malignant	4 (9.5)

Categorical variables (*n* [%]) and continuous variables (mean±SD). BMI: Body mass index, IFG: Impaired fasting glucose, SD: Standard deviation

palpable in 19% of patients. Hypertension was present in 54.8% of patients.

Tumor location and characteristics

Of the all adrenal masses, the majority (95.2%; *n* = 40) of patients were unilateral and left-sided (50%; *n* = 21) tumors; 4.8% of patients had bilateral adrenal mass. The tumor was benign in 38 (90.5%) patients and malignant in 9.5% of patients. One patient each had metastases to liver and lungs. Most of the tumors were large, i.e., >4 cm in 42.8% of cases.

Biochemical characteristics

All patients had a hormonal evaluation for Cushing's syndrome and pheochromocytoma, whereas ARR was done in patients with hypertension/hypokalemia. Twenty patients had nonsecretory lesions, of which 13 patients had nonfunctional adrenal adenoma, five patients had myelolipoma, and one patient each had adrenal cyst and lymphoma. SCS was present in 7.1% of patients. Of the secretory lesions, 26.2% of patients had pheochromocytoma, three patients each with primary hyperaldosteronism and Cushing's syndrome, and two patients had ACC, as shown in Table 2.

Radiological tests

CT scan of the abdomen with the adrenal protocol was used to localize the tumor in all our patients. Four patients had evidence of malignancy as judged by the presence of metastasis to lungs/liver and locoregional spread.

Preoperative preparation

All patients having pheochromocytoma received alpha-blocker, followed by beta-blocker before the operation. Preoperative correction of the intravascular volume was done in all patients. Of the 27 patients in whom adrenalectomy was documented, open procedure was done in 63% and laparoscopic in 37% of patients.

Patient outcome

The overall surgical cure was achieved in 74.1% (*n* = 20), with 100% cure in nonfunctional adrenal adenoma, myelolipoma, and SCS. Four patients required redo surgery, as shown in Table 3.

Factors predicting functional lesion

The factors which differentiated function adrenal masses from nonfunctional were younger age at presentation (≤40 years), obesity, symptomatic presentation, and small tumor diameter, whereas on multivariate analysis, only patients aged ≤40 years at presentation predicted the functional lesion, as shown in Table 4.

Table 2: Hormonal and radiological characteristics of patients with an adrenal mass

Characteristic	Number of patients (%)
Hormone secretion	
Nonsecretory lesion	20 (47.6)
Nonfunctional adrenal adenoma	13 (30.9)
Myelolipoma	5 (11.9)
Adrenal cyst	1 (2.4)
Adrenal lymphoma	1 (2.4)
Functional lesion	22 (52.4)
Pheochromocytoma	11 (26.2)
Primary hyperaldosteronism	3 (7.1)
ACC	2 (4.7)
Subclinical Cushing's syndrome	3 (7.1)
Cushing's syndrome	3 (7.1)
Radiological	
Location of lesion	
Right	19 (45.2)
Left	21 (50.0)
Bilateral	2 (4.8)
Size of lesion >4 cm	18 (42.8)
Surgical cure *n*=27	20 (74.1)

Categorical variables (*n* [%]). ACC: Adrenocortical carcinoma

Table 3: Favorable surgical outcome of patients with an adrenal mass

Characteristic	Surgery	Outcome	Redo-surgery
Overall	27 (64.3)	20 (74.1)	
Nonfunctional adrenal adenoma	4 (30.8)	4 (100.0)	
Subclinical Cushing's syndrome	2 (66.7)	2 (100.0)	
Primary hyperaldosteronism	3 (100.0)	1 (33.3)	1 (33.3)
Cushing's syndrome	3 (100.0)	2 (66.7)	1 (33.3)
Pheochromocytoma	11 (100.0)	8 (72.7)	1 (9.0)
Myelolipoma	2 (40.0)	2 (100.0)	
ACC	2 (100.0)	1 (50.0)	1 (50.0)
Adrenal cyst	0		

Categorical variables (*n* [%]). ACC: Adrenocortical carcinoma

Discussion

Modern imaging modalities have made adrenal mass a common occurrence in clinical practice. Although the adrenal mass can have an extensive differential diagnosis, nonsecreting cortical adenomas (75%) account for the majority. The prevalence of various adrenal masses varies between surgical series.[9,22] The optimal management of an adrenal mass is to rule out malignancy from the lesions and to identify the functioning from the nonfunctioning tumors.[10]

Our study involved a retrospective review of the clinical characteristics and outcome of 42 patients with adrenal masses. The mean age was 45.2 ± 12.4 years, with a female predominance. Symptomatic adrenal mass (52.4%) was the most common mode of presentation. Abdominal pain and hypertension were the most common presenting symptoms. Obesity and dyslipidemia were present in half of the patients and hyperglycemia in 23.8%. Majority of tumors were benign (90.5%). Most of the adrenals lesions were nonfunctional (47.6%), followed by

Table 4: Characteristics of patients with an adrenal mass divided on the basis of functionality

Characteristic	Functional (*n*=22)	Nonfunctional (*n*=20)	*P**	
			Univariate	Multivariate
Age ≤40 years	15 (68.2)	4 (20.0)	0.002	0.046
Females	18 (81.8)	11 (55.0)	0.064	
BMI	27.2±3.5	24.1±4.6	0.018	0.070
Incidental presentation	7 (31.8)	13 (65.0)	0.033	0.086
Hypertension	15 (68.2)	8 (40.0)	0.070	
Hyperglycemia	7 (31.8)	3 (15.0)	0.207	
IFG	4 (57.1)	1 (33.3)		
Diabetes	3 (42.9)	2 (66.7)		
Obesity	15 (68.2)	7 (35.0)	0.034	0.094
Dyslipidemia	12 (54.5)	8 (40.0)	0.353	
Tumor diameter	3.6±1.6	4.7±1.8	0.042	0.294
Size of lesion >4 cm	6 (27.3)	12 (60.0)	0.034	0.137
Malignancy	4 (14.8)	0	0.121	

Categorical variables (*n* [%]) and continuous variables (mean±SD). *P<0.05 is considered statistically significant. BMI: Body mass index, IFG: Impaired fasting glucose, SD: Standard deviation

pheochromocytoma (26.2%), as shown in Table 2. Lesions were equally distributed on either side, with slight left predominance. Most of the lesions were large (>4 cm). The surgical cure was achieved in 74.1% of patients, with good outcome in nonfunctional adrenal adenoma, myelolipoma, and SCS. Age ≤40 years was predictive of the functional adrenal mass.

The size of the lesion is also indicative of its etiology, with higher chances of malignancy in larger tumors. A cutoff of 4 cm is an accepted size, beyond which suspicion of malignancy should increase.[23] In a study by Giordano R, et al., 118 patients of adrenal masses with initial tumors size of 2.22 cm, an increase in the tumor size occurred in seven patients and a decrease in size was noted in two patients, when followed up for 3 years. Furthermore, no malignancy was noted in tumor smaller than 4 cm in this series.[24] Herrera *et al*.[25] reported a malignancy rate of only 1.5% in their series of 342 patients and all were >5 cm in size.

Various studies have shown the mean age of the presentation is between fifth to sixth decade, with female preponderance.[5,16,26,27] The younger age at presentation in our study could be because many adrenal masses were functional lesions, which are known to present at a younger age. The clinical presentation of adrenal mass varies, with abdominal pain being the most common presentation. The study by Khanna *et al*.[16] reported pain abdomen in 57.14% of patients. The study by Li *et al*.[15] showed that a significant number of patients had hypertension (53.9%), dyslipidemia (29.8%), and diabetes (13.3%), as was seen in our study.

Left side predominance has been seen by many studies,[18,26] contrary to other reports.[6,28] However, in our study, the left adrenal gland was more frequently affected; this could likely be due to the diagnostic modality used. Mantero *et al*.[6] used ultrasonography as their diagnostic technique and found right predominance, as this imaging allows for greater visualization of the right adrenal gland than the left.[29] However, no difference in location was apparent in studies for evaluating adrenal mass using CT scans[25,30] or at autopsy.[2]

The percentage of various etiologies for adrenal mass varies by study, due to differences in selection criteria and referral bias. The prevalence of pheochromocytoma varies between 1.5% and 23% and that of ACC is 1.2%–12%.[31] In a Korean study,[32] the prevalence of functioning adrenal tumors reported was reported to be as high as 41.0%, as was seen in our study.

Pheochromocytoma was seen in a higher number of patients in our study as compared to world literature, which could be because of referral bias; however, other studies[14,32] also revealed pheochromocytoma in around 20% of the adrenal mass patients. In another study, the prevalence of subclinical Cushing's and Cushing's syndrome were slightly higher compared to those in our study.[33] In our study, >70% of pheochromocytoma patients were deemed as cured (biochemically and/or radiologically), which is similar to results reported in other studies (79%–92.6%).[34,35]

One series reported that older patients were more likely to develop hormonal hyperfunction, although the association was not significant.[36] Several studies demonstrated that tumor size >3 cm at diagnosis was related to the occurrence of hormonal hyperfunction.[36,37] The Korean study reported that age, tumor size, number, and location showed no statistical significance as risk factors for functioning tumors.[32] Another study also revealed that age, BMI, tumor size, number, and location were not independent risk factors for functional tumors.[18] Kim *et al*.[37] in their study revealed that BMI, fasting glucose, HbA1c, total cholesterol and presence of type 2 diabetes,

and hypertension were significantly higher in patients with SCS in comparison with those with nonfunctioning tumors. However, interpretation of these data has to be considered with caution because of the possibility of confounding and referral bias.

This study has several limitations, including that it was a retrospective review of cases from a single-center and the sample size was small. There was a lack of proper clinical and biochemical follow-up of some patients.

Conclusion

A significant proportion of patients have functional tumors. Pheochromocytomas (26.3%) were the most frequently observed, followed by primary hyperaldosteronism (7.1%). The surgical cure was achieved in 74.1% of patients. Patients with functional lesions were comparatively young (≤40 years) as compared to nonfunctional. Surgery is required in all the functional adrenal masses and large adenomas. Benign lesions, when excised completely, result in excellent long-term outcome. Further, prospective studies with large sample size and long-term follow-up are required to address this issue.

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Conflicts of interest

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