Original Article

Adrenal tumors: An experience of 10 years in a single surgical unit

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Abstract

INTRODUCTION: Most of the adrenal masses are discovered incidentally by imaging techniques for reasons unrelated to adrenal diseases. Treatment is based on various factors such as, nature of adrenal mass, age of presentation, size of tumor, and the functional status of tumor. We report a series of 14 consecutive cases of adrenal tumors treated in a single surgical unit in our hospital. **AIM:** The aim of this study was to evaluate the clinical profile and outcome of treatment of adrenal tumors treated in a surgical unit. **MATERIALS AND METHODS:** It is a retrospective study data of 14 cases of adrenal tumors treated in a single surgical unit in University Hospital over 10 years have been analyzed. Various parameters such as gender, age, size of tumor, functional status, histopathology, type of management, and outcome have been reviewed. **RESULTS:** A total of 14 patients with adrenal masses were seen over a 10 year period (1997-2006). All were referred cases, either from endocrinology or medicine wards. There were seven female and seven male patients. Mean age of patients was 48.6 years (range 14-60 years). Mean size of tumor was 8.0 cm (5.9 cm for benign tumors and 9.7 cm for malignant tumors). There were six cases of adrenal carcinoma, four cases of adrenal myelolipoma, two cases of pheochromocytoma, and one each case of adrenal hyperplasia and histoplasmosis. There were only two functional tumors. All, except two malignant cases were treated operatively. A total of 5 year survival was 100% in benign cases and 27% in malignant tumors. **CONCLUSION:** Adrenal tumors need to be assessed for their functional status and malignant potential prior to treatment. Surgical excision is usually curative for benign lesion. Among malignant tumors the benefits of surgery depend on local extent and metastatic status of tumors.

Key Words: Adrenal, adrenalectomy, incidentalomas

Introduction

Early diagnosis and management of adrenal tumors has undergone a significant change with the advances in biochemical evaluation, diagnostic imaging techniques, and progress in the field of minimally invasive surgery. Appropriate assessment of an adrenal mass is an essential prerequisite prior to its definitive treatment. An adrenal mass, which is unexpectedly detected through an imaging procedure performed for reasons unrelated to adrenal dysfunction or suspected dysfunction is known as adrenal incidentaloma.[1] Its prevalence at autopsy ranges from 1.4% to 2.9%. Screening with ultrasound identifies incidentalomas in 0.1% population with general good health. Aging is associated with increased frequency, prevalence being <1% among individuals less than 30 years of age to about 7% in those over 70 years of age.[2]

While treating adrenal tumors it should be remembered that the cortex and the medulla have different embryonic origin and accordingly have different structure and function and develop different tumors. It should also be borne in mind that tumors vary in their functional status. The incidence of malignancy increases with the increase in size of the tumor.[2] With the life expectancy increasing, more adrenal masses are likely to be detected incidentally; hence, studies with a long follow-up are needed to develop guidelines for the appropriate management of these tumors. The most effective imaging modality for evaluation of an adrenal mass is the contrast enhanced computed tomography (CECT) scan. Perinephric fat allows the gland to be clearly displayed and even 1 cm size tumors can be detected with 100% sensitivity.[3] For initial evaluation of an adrenal mass, Favia *et al*.[4] have suggested a panel of biochemical tests such as baseline plasma cortisol level, plasma aldosterone and plasma renin activity, serum dihydroepiandrosterone sulfate (DHEA-S) concentration and 24-h urinary epinephrine and norepinephrine, metanephrine and vaniyl mandelic acid. The literature supports that the overnight 1 mg dexamethasone suppression test appears to be the test of choice to rule out autonomous glucocorticoid production, Cushing's syndrome or subclinical Cushing's syndrome.[5]

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Materials and Methods

This is a retrospective study of prospectively collected data of 14 patients with 16 adrenal masses treated in a single surgical unit of our University Hospital over 10 years (1997-2006) with a 5 year follow-up. All were detected on ultrasonographic or computed tomography (CT) scan examination of the abdomen and referred to our hospital and the demographic and clinical profiles of the patients were recorded. The tumor profile, treatment offered and follow-up outcome were studied. Hormonal studies were performed in all cases, which included plasma cortisol measurement, 1 mg overnight dexamethasone suppression test, serum testosterone, 24 h urinary metanephrine, catecholamines and vanillylmandelic acid, plasma catecholamines, serum DHEA. In one patient, who presented with thyrotoxicosis, hepatospleenomegaly and a left sided adrenal mass, ultrasound guided fine needle aspiration cytology (FNAC) was performed after ruling out pheochromocytoma. Twelve patients were given operative treatment while two patients with advanced malignancy were treated conservatively. All were operated by a transabdominal subcostal approach. All specimens were sent for histopathology. Postoperative follow-up included clinical examination for every 3 months, sonographic evaluation for every 6 months, and CT scan once a year for the first 2 years.

Results

During the 10 year period from January 1997 to December 2006, 14 patients with adrenal tumor were treated in our unit. All were referred cases from endocrine or medicine wards. Out of these, seven were males and an equal number of females. Seven patients had tumors on the

right side and five patients had tumors on the left while two patients had bilateral tumors. Hence, a total of 16 tumors were treated. Mean age of the patients were 48.6 years (range 17-60 years). Mean size of tumor was 8.0 cm (range 3.0-12.6 cm). Benign tumors were comparatively smaller (average 5.9 cm) than malignant tumors (average 9.7 cm).

The clinical presentation was varied, abdominal pain being the most common presentation (57.14%). Anorexia and weight loss were the second most common presentation (28.57%). Ascites, virilization, blurring of vision and palpitation, hypertension with hypertensive retinopathy were other presentations [Table 1]. Ascites was present in two patients, both with malignant disease. Two patients of pheochromocytoma had hypertension on presentation while one of them presented with blurring of vision because of grade IV hypertensive retinopathy, that is, bilateral papilledema, hemorrhagic spots, arteriolar, and venular attenuation with exudates. CT scan abdomen showed appearance consistent with bilateral pheochromocytoma with maintained fat planes. 24 h urinary vaniyl mendalic acid (VMA) was 27.3 mg/day (normal 0.4-15.4 mg/day). After controlling blood pressure, initially with prazocin (alpha blocker) and nifedipine (calcium channel blocker) and later metoprolol (beta blocker) the patient underwent adrenalectomy. There was no intraoperative rise of blood pressure. Histopathology report revealed bilateral malignancy with extensive necrosis. It was chromogranin A positive on immunohistochemistry. Another patient presented with hepatosplenomegaly thyrotoxicosis with adrenal mass. FNAC performed preoperatively did not give any conclusive diagnosis. He underwent splenectomy with liver biopsy with removal of adrenal tumor. Histopathology revealed histoplasmosis. He was further treated with amphotericin B. Six patients had malignant tumors. The mean size of carcinoma was greater than that of benign tumors (9.7 vs. 5.9 cm). Twelve patients underwent adrenalectomy by transabdominal subcostal approach. Two patients with advanced malignancy did not undergo surgical intervention. All specimens were sent for histopathology. The details of tumor profile are included in Table 2.

The patients could be maximally followed-up for 7 years and the 5 year survival rate for benign tumors was 100% while it was only 27% for malignant tumors.

Table 1: Clinical presentation of the adrenal masses

Symptoms	Number of patients (%)
Abdominal pain	8 (57.14)
Anorexia/weight loss	4 (28.57)
Ascites	2 (14.28)
Blurring of vision	1 (7.14)
Thyrotoxicosis	1 (7.14)
Virilization	1 (7.14)
Hypertension	2 (14.28)

Table 2: Details of the tumor characteristics

Mean size of tumor	8.0 cm (3.0-12.6)
Benign tumor	5.9 cm (3.0-12.6)
Malignant tumor	9.7 cm (8.0-12.6)
Right side tumor	7
Left side tumor	5
Bilateral	2
Histological diagnosis	
Carcinoma	6
Myelolipoma	4
Hyperplasia	1
Pheochromocytoma (adrenal)	2
Histoplasmosis	1
Hormonally active tumor	2
Operative intervention	12
Benign tumor	8
Malignant tumor	4
Mean hospital stay	5 days (3-7 days)
5 year survival (%)	
Benign	100
Malignant	27

Discussion

Although, the differential diagnosis of an adrenal mass is extensive, non-secreting cortical adenomas account for majority of tumors (41%), others' being metastases (19%), adrenocortical carcinoma (10%), myelolipoma (9%), pheochromocytoma (8%), benign lesions like adrenal cysts forming the remainder.[6] In our series, maximum were carcinoma probably because all were referred cases. The optimal management of an adrenal tumor is aimed at identifying the malignant tumors from the benign lesions and the functioning from the non-functioning tumors. This is carried out by evaluation of the clinicopathological features, biochemical tests, and anatomical features demonstrated on CT or magnetic resonance imaging (MRI) scan. Most adrenal tumors are non-hypersecreting however, the following endocrine features may suggest subclinical hypercortisolism: High borderline free cortisol excretion, impaired cortisol rhythm, partial cortisol suppression with dexamethasone, low plasma adrenocorticotrophic hormone (ACTH), and unresponsiveness to corticotrophin releasing hormone.[7-9]

Size of the lesion also gives an indication of its etiology, the chances of malignancy being higher in larger tumors. In our experience also, the mean size of malignant tumors was 9.7 cm as compared to 5.9 cm in the benign group. A reasonable accepted cut-off value is 4 cm, beyond, which strong suspicion of malignancy should be entertained.[10] In a study by Giordano *et al*.,118 patients were followed-up for an average of 3 years, an increase in the size of adrenal masses was noted in only 7 patients and a decrease in size occurred in 2 patients when the initial average size of tumors was 2.22 cm. Another significant correlation, which can be deduced is that there was no malignant tumor in a series of 118 patients, the average size being smaller than 4 cm.[11] Herrera *et al*.[12] reported only 1.5% rate of malignancy in their series of 342 patients and all were greater than 5 cm in size. Candel *et al*.[13] found that 97% of lesions larger than 3 cm in size were malignant while 87% of lesions smaller

than 3 cm were benign in nature. The bilaterality of tumors suggest several diagnosis, which includes metastatic disease, congenital adrenal hyperplasia, lymphoma, infection, for example, tuberculosis, fungal, hemorrhage, ACTH dependent Cushing syndrome, pheochromocytoma, amyloidosis, infiltrative disease of the adrenal gland.

Ultrasonography (USG) can detect adrenal masses greater than 2 cm however, it does not allow accurate assessment of morphology and it may be used for follow-up evaluation of patients.[14] In CECT scan perinephric fat allows better visualization of the gland and 1 cm size lesion can be detected with 100% sensitivity.[3] Benign tumors appear as smooth homogenous masses of low density with little contrast enhancement. A homogenous mass with a low attenuation value (<10 Hounsfield units [HU]) on a CT scan is likely to be a benign adenoma. Malignant lesions appear to be larger with irregular margins and heterogeneous density. Myelolipoma exhibit a non-functioning tumor composed of fat and bone marrow elements. Metastatic deposits from other primary are often bilateral with irregular margins and irregular enhancement. A threshold of 10 HU and 24 HU with a 14 min delay on a CECT scan are used as cut off values to distinguish between adenomas and metastasis.[15]

MRI has high sensitivity and specificity. Dynamic gadolinium enhanced studies give more reliance to MRI scans. Imaging performed 36-48 h after meta-iodobenzylguanidine (MIBG) injection (meta iodobenzlguanidine) is useful for detection of pheochromocytoma.[16]

Positron emission tomography (PET) scan is another promising technique for studying adrenal masses.[8] PET imaging with 18-F flurodeoxyglucose is a useful modality. Benign tumors do not show uptake pattern while metastasis show high uptake with 100% sensitivity and specificity. Whole body PET scan can show extra-adrenal involvement.

All patients must undergo systematic hormonal assessment after a complete history and clinical examination. Hormonal evaluation includes morning and midnight plasma cortisol measurements, 1 mg overnight dexamethasone suppression test, 24 h urinary excretion of catecholamines, metanephrines or plasma free metanephrines. When patient presents with hypertension, serum potassium, plasma aldosterone, plasma renin activity are especially helpful. Serum DHEA, testosterone or 17-beta-hydroxyl estradiolare carried out to assess a virilizing or feminizing tumor. Favia *et al*. have suggested the following tests to be conducted in all patients of incidentalomas: (1) Baseline plasma cortisol levels; (2) plasma aldosterone and plasma rennin activity; (3) serum DHEA-S concentration; and (4) 24 h urinary epinephrine and nor-epinephrine.[4]

Fine needle biopsy is currently not recommended for the routine work-up of patients with adrenal tumors. According to National Institutes of Health (NIH) guidelines, CT guided Fine Needle Aspiration (FNA) may be helpful in diagnostic evaluation of patients with a history of cancer especially lung, breast and kidney with no other signs of metastases and a heterogeneous adrenal mass with a high attenuation value (greater than 20 HU). Pheochromocytoma should always be excluded before attempting FNA of an adrenal mass in order to avoid the potential for hypertensive crisis.

Four of our cases were diagnosed on CT scan to be myelolipoma. Gierke in described a lesion of adrenal gland containing fat and myeloid elements.[17] The term "myelolipoma" was first used by Oberling in 1929.[18] Majority of these tumors are asymptomatic, small benign lesions of the adrenal cortex [Figure 1]. Prognosis of myelolipoma is excellent. It does not usually undergo malignant change.[18] As lesions larger than 10 cm have a risk of internal hemorrhage, these should be removed. However, lesions smaller than 6 cm can be followed-up for 6-12 months.[19,20]

Some rare genetic syndromes which predispose to adrenocortical tumors include Beckwith–Weidman syndrome (over expression of Insulin-like growth factor IGF-II), Li-Fraumeni syndrome (germline mutation in p53 tumor suppressor gene), multiple endocrine neoplasia -I MEN-I, Carney complex and Mc-Gene–Albright syndrome.

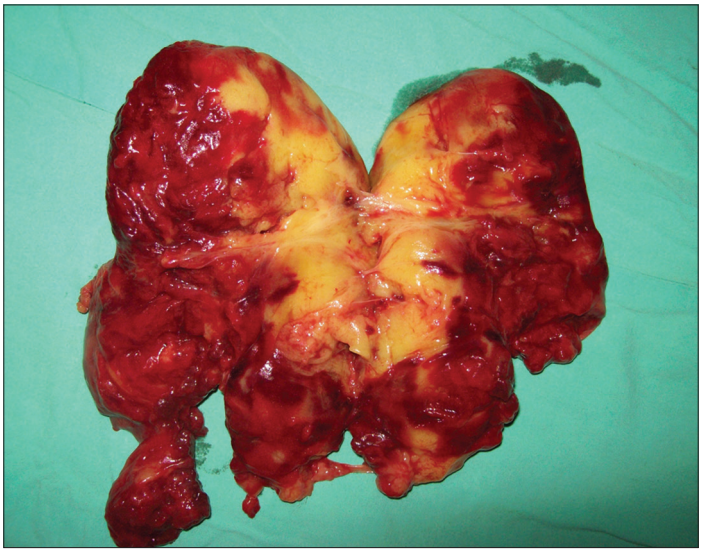

Figure 1: Adrenal myelolipoma

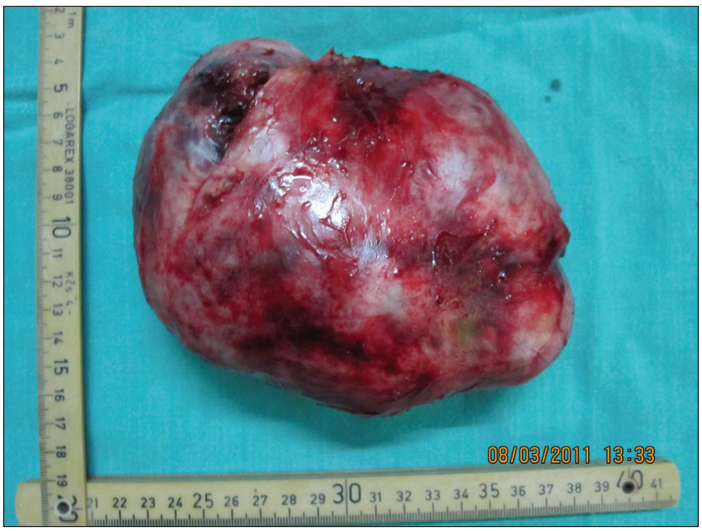

Figure 2: Adrenocortical carcinoma

The Asian histoplasmosis, as described by Symmers,[21] is characterized by painful ulceration of mucocutaneous junction and liability to acute adrenocortical insufficiency. Our patient presented with unilateral adrenal mass with hepatosplenomegaly. It appears that he developed disseminated histoplasmosis followed by resolution of the lesion in various organs however, it remained localized in the left adrenal gland. Thyrotoxicosis appears to be unrelated to histoplamosis infection.[22]

The world-wide annual incidence of adrenocortical carcinoma is 1 per million and accounts for 0.2% of all cancer related deaths.[23] Adrenocortical carcinoma may be functional with a clinically endocrine syndrome like Cushing's or it may be mixed syndrome as Cushing's with virilization.[24] Virilization is due to dehydroepiandrosterone and dehydroepiandrosterone sulfate rather than testosterone. Adrenocortical carcinoma is a rare neoplasm with poor prognosis [Figure 2]. It has to be differentiated from adenoma, pheochromocytoma or a renal cell carcinoma infiltrating the adrenal gland. Tumor, if more than 95 g is usually malignant.[25] Pheochromocytoma will usually present with hypertension and increased catecholamine levels in the serum with immunohistochemical markers like chromogranin. The presence of glands with red blood cells and abundant cytoplasmic glycogen and positivity for immunohistochemical markers such as cytokeratin and Epithelial Membrane Antigen (EMA) will favor renal cell carcinoma.

Icard *et al*.[26] advocated that nephrectomy would help to decrease the high recurrence rate of adrenocortical carcinoma, as it would allow wide operative margins and avoid violating the tumor anatomic space, however, this opinion has not been validated by clinical studies. The involvement of adjacent organs, renal vein or inferior vena cava (IVC) is frequent in adrenocortical carcinoma and represents a poor prognostic feature. The feasibility and efficacy of complete resection for adrenocortical carcinoma extending into these organs is questionable but can be associated with prolonged survival.

A larger series with a long follow-up is needed to be able to develop a proper protocol for a systematic follow-up of these patients. In our series, maximum follow-up is 7 years and it suggests a good prognosis for benign tumors.

Conclusion

Most of the patients being referred were of large size (>4 cm). Malignancy and myelolipoma formed the majority of the patients. Functional abnormalities were detected in only 14.8% of patients. A total of 5 year survival was 100% in benign cases and only 27% in malignant cases.

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