

# Adrenal Incidentaloma Needs thorough Biochemical Evaluation – An Institutional Experience

Akash N. Shah, Uma K. Saikia, Bipul K. Chaudhary, Ashok K. Bhuyan

Department of Endocrinology, Gauhati Medical College and Hospital, Guwahati, Assam, India

## Abstract

**Context:** Adrenal incidentalomas (AIs) are seen in around 2% of apparently healthy individuals. These require careful evaluation for the hormone excess state and the presence of malignancy prior to intervention. **Aims:** To study the clinical, biochemical, and imaging characteristics of the patients with AI and correlate the diagnosis with the histopathology findings in patients undergoing surgery. **Settings and Design:** Retrospective observational study. **Methods and Material:** Patients with adrenal incidentaloma presenting between January 2017 and January 2021 were evaluated as per guidelines provided by the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors. Patients were given final diagnosis on the basis of imaging impression, hormonal activity, and biopsy results (when applicable). **Results:** Forty-eight patients were evaluated, with 25 being male, the mean age being 40.9 years (8–71), and the mean size of the mass being 6.21 (1.4–13.7) cm. Thirty-five (72.9%) of them underwent surgical excision. The most common diagnosis was myelolipoma (16), followed by pheochromocytoma (10) and adenoma (9). Nineteen patients were found to have hormone-secreting masses. Two patients with pheochromocytoma were normotensive. There was discordance between imaging diagnosis and hormonal status in two patients, with final diagnosis of pheochromocytoma. One patient with extramedullary erythropoiesis of the adrenal gland was subsequently diagnosed with sickle cell anemia and adrenal insufficiency. **Conclusions:** The study highlights the rare possibility of discrepancy between non-contrast CT diagnosis and functional status of AI. There is also a rare possibility of extramedullary erythropoiesis presenting as AI with adrenal insufficiency. Specific evaluation for such rare possibilities should be considered in AI cases as per clinical scenario.

**Keywords:** Adenoma, adrenal incidentaloma, adrenal insufficiency, adrenocortical carcinoma, myelolipoma, pheochromocytoma

## INTRODUCTION

An adrenal incidentaloma (AI) is defined as a clinically unapparent adrenal mass greater than 1 cm in diameter detected during imaging performed for reasons other than those for suspected adrenal disease.<sup>[1]</sup> The term “incidentaloma” was coined in 1982 by Geelhoed and Druy,<sup>[2]</sup> who recognized that with the advent of improved resolution of radiological techniques, the clinicians were faced with a new challenge and an unfamiliar dilemma of early diagnosis of an asymptomatic adrenal mass. The strict definition, recognized by the European Society of Endocrinology and European Network for the Study of Adrenal Tumors (ESE/ENSAT), excludes adrenal lesions discovered during the screening of patients with hereditary syndromes or extra-adrenal tumors.<sup>[1]</sup> As per current guidelines, incidentally discovered adrenal lesions with a diameter < 1 cm do not warrant further investigation, unless clinically indicated.<sup>[1,3]</sup>

Autopsy studies suggest a prevalence of AI of around 2% (range 1.0–8.7%),<sup>[4,5]</sup> which increases with age, whereas radiological studies report a frequency of around 3% in the age of 50 years, which increases up to 10% in the elderly.<sup>[4-7]</sup> Large studies have reported adenoma to be the most common diagnosis in cases of AI (33–96%), of which non-functioning adenoma is the most common diagnosis. Other important causes include pheochromocytoma (1.5–14%), adrenocortical carcinoma (ACC) (1.2–11%), myelolipoma (7–15%), and metastasis (0–18%).<sup>[5,6,8]</sup>

**Address for correspondence:** Dr. Ashok K. Bhuyan,

Department of Endocrinology, Super Speciality Building, Gauhati Medical College and Hospital, Bhangagarh, Guwahati, Assam 781032, India.

E-mail: ashokbhuyan27@gmail.com

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The major issues of concern in AI include functionality and potential for malignancy upon which the need for surgery is decided. Hence, appropriate evaluation is needed to decide on the further management and follow-up.

## AIM AND OBJECTIVE

- To study the clinical, biochemical, and imaging characteristics of the patients with AI and correlate the diagnosis with the histopathology findings in patients undergoing surgery.

## METHODOLOGY

Patients with AI presenting to the Endocrinology Department of Gauhati Medical College and Hospital between January 2017 and January 2021 were evaluated as per ESE and ENSAT guidelines on AI. The data were retrospectively evaluated for this study. The study was approved by the institute ethical committee. Any patient with incidentally detected adrenal mass was subjected to clinical evaluation for symptoms and signs suggestive of any hormonal excess or adrenal insufficiency, followed by appropriate biochemical evaluation. All patients were screened for sub-clinical Cushing's syndrome by 1 mg overnight dexamethasone suppression test (ONDST). Patients were labelled as having "autonomous cortisol secretion" or "sub-clinical Cushing's syndrome" if the measured serum cortisol after ONDST was > 5.0 mcg/dl. If the serum cortisol after ONDST was > 1.8 mcg/dl and < 5.0 mcg/dl, patients were labelled as having "possible autonomous cortisol secretion".<sup>[1]</sup> Patients were also screened with 24 hour urine metanephrines or plasma-free metanephrines for pheochromocytoma.

Hypertension was defined as a systolic blood pressure (SBP) greater than or equal to 140 mm Hg or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg as defined by the European Society of Hypertension Guidelines.<sup>[9]</sup> Resistant hypertension was defined as a blood pressure greater than 140/90 mm Hg in spite of the concurrent use of three anti-hypertensive agents of different classes at pharmacologically effective doses or controlled BP (<140/90) on four or more anti-hypertensive agents.<sup>[10]</sup> In hypertensive patients, plasma aldosterone concentration (PAC) and plasma renin activity (PRA) evaluation was considered, and in those with a ratio more than 10 ng/dl per ng/ml/hr, patients were subjected to saline suppression test. Those with post-saline suppression, PAC > 10 ng/dl was considered to be primary aldosteronism.<sup>[11]</sup> In suspected cases of adrenocortical carcinoma (ACC), serum dehydroepiandrosterone sulfate (DHEAS) was evaluated. Accordingly, biochemical diagnosis was assigned to each case.

All patients were subjected to non-contrast enhanced computed tomography (CT) scan of the abdomen (if not already performed) and were further evaluated with contrast-enhanced CT scan if indicated. Depending upon non-contrast enhancement values and wash-out values, patients were given an imaging diagnosis.

Patients with pheochromocytoma, those with ACC, and those with a size of adrenal mass > 4 cm were considered for surgical resection of adrenal mass, and biopsy of the mass was performed. Patients with elevated urinary metanephrines or normetanephrine were prepared with alpha and beta blockers as suggested by the Endocrine Society clinical practice guidelines.<sup>[12]</sup> Appropriate biochemical follow-up was performed. Patients were given final diagnosis on the basis of imaging impression, hormonal parameters, and histopathology results (when applicable).

The estimation of serum cortisol was performed by electrochemiluminescence. The plasma adrenocorticotrophic hormone, plasma renin activity, and plasma aldosterone concentration were estimated using chemiluminescence assay with competitive methods. Urinary metanephrines were estimated by the enzyme-linked immunosorbent assay method. The inter-assay and intra-assay coefficients of variation for all tests were < 10% and < 15%, respectively.

## RESULTS

In the present study, we included analysis of 48 subjects with AI and evaluated a total of 54 masses. Out of these, 35 subjects underwent the operative procedure, and biopsy results were available for 35 masses. The baseline characteristics are described in Table 1.

Among the study population, 21 subjects had hypertension, out of which four subjects had resistant hypertension, eight subjects had diabetes mellitus, and 9 subjects were obese. The most common incidentaloma found in our study was myelolipoma (33.33%), followed by pheochromocytoma (20.8%) and adrenal adenoma (18.75%). The following cases were included in the group 'others': two cases with extramedullary erythropoiesis, two with lymphoma, one with hemorrhagic cyst, and one with cyst. Distribution of subjects as per diagnosis and comorbidities is described in Table 2.

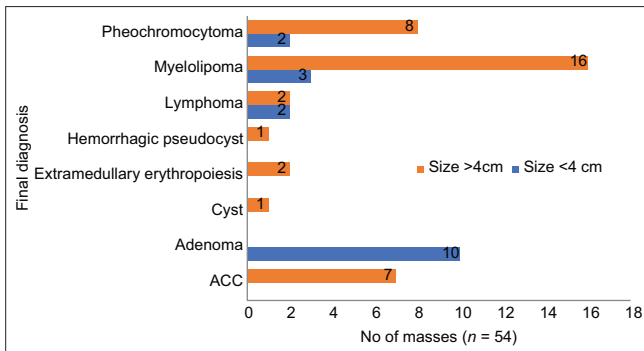
Six subjects were found to have bilateral masses, whereas 22 had mass on the left side and 20 had mass on the right side. Two different pathologies were not encountered in those subjects with bilateral masses.

**Table 1: Baseline characteristics**

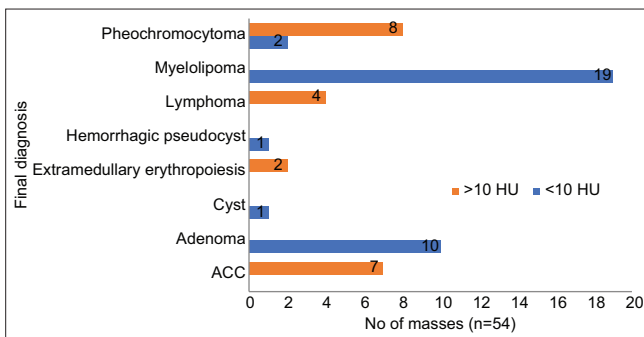
Total number of patients	48
Total number of masses evaluated	54
Males	25 (52.08%)
Females	23 (47.92%)
Mean age (years)	40.9 (8-71)
Imaging carried out for the pain abdomen	36 (75%)
Hypertension	21 (43.75%)
Diabetes mellitus	8 (16.67%)
Obesity	9 (18.75%)
Mean size of the mass (cm)	6.21 (1.4-13.7)
Excision	35 (72.9%)

**Table 2: Diagnosis-wise distribution of subjects and associated comorbidities (n=48)†**

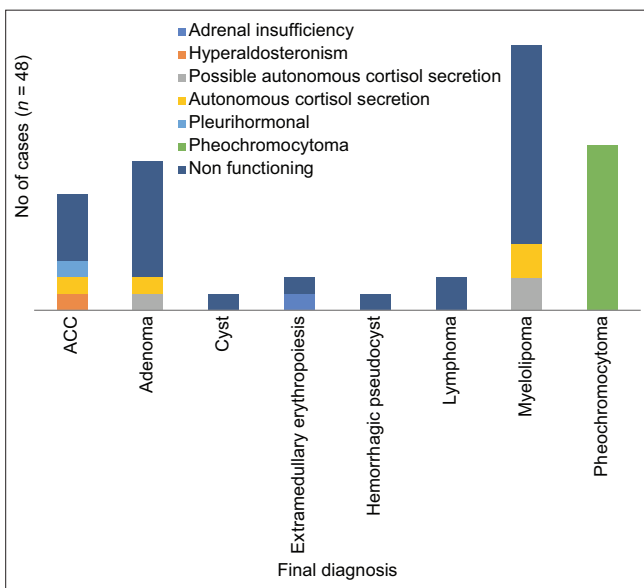
Diagnosis	No (%)	HTN (21)	Resist HTN (4)	Diabetes mellitus (8)	Obesity (9)
ACC	7 (14.58%)	3 (14.28%)	0	1 (12.5%)	0
Adenoma	9 (18.75%)	2 (9.52%)	0	2 (25%)	3 (33.33%)
Myelolipoma	16 (33.33%)	7 (33.33%)	0	3 (37.5%)	6 (66.66%)
Pheochromocytoma	10 (20.83%)	8 (38.09%)	4 (100%)	2 (25%)	0
Others	6 (12.5%)	1 (4.76%)	0	0	0



**Figure 1:** Distribution of masses on the basis of size



**Figure 2:** Distribution on the basis of CT characteristics (Hounsfield units)



**Figure 3:** Distribution on the basis of functional status

Out of the masses evaluated, 35 were larger than 4 cm in size, whereas 17 were smaller than 4 cm in size [Figure 1].

All myelolipomas and adenomas were found to have < 10 HU on non-contrast CT. All adrenocortical carcinoma and lymphomas were found to have > 10 HU on non-contrast CT. However, two out of 10 pheochromocytoma cases had attenuation value < 10 HU on non-contrast CT [Figure 2].

Autonomous cortisol secretion was seen in two patients with myelolipoma and one patient each with adrenocortical carcinoma and adenoma, while possible autonomous cortisol secretion was seen in two patients with myelolipoma and one patient with adrenal adenoma. Among patients with autonomous and possible autonomous cortisol secretion, two patients had hypertension with obesity and type 2 DM, one patient had hypertension, one patient had obesity with type 2 DM, and two patients had obesity [Figure 3].

Hyperaldosteronism was detected in one patient with ACC. Adrenal androgen secretion with glucocorticoid excess was seen in one patient with ACC. Adrenal insufficiency was a manifestation in one patient of extramedullary erythropoiesis due to sickle cell anemia [Figure 3].

## DISCUSSION

Comprehensive clinical practice guidelines have been provided by ESE and ENSAT on the management of AI.<sup>[1]</sup> In the present study, we have described 48 subjects with a total of 54 AIs, who were evaluated as per ESE and ENSAT guidelines.

The salient features of the current study are compared with those of other studies in Table 3.

The mean age from various studies with AIs has been found to be 57.5 years.<sup>[19]</sup> In the present study, the mean age was 40.9 years.

The functional status of AIs influences the decision regarding surgical management, appropriate pre-operative preparation, and long-term follow-up of the patients. On evaluation of the functional status, studies have shown that 10–15% of AIs secrete hormones in excess.<sup>[13]</sup> Hormone-secreting incidentalomas were seen in 39.5% of masses in the present study.

Hypertension is a common sign of pheochromocytoma, but 5–15% of patients may have normal blood pressure at presentation. This is more commonly seen in those

**Table 3: Comparison of salient features with other large studies**

	Current study	Other studies
Mean age (years)	40.9	57.5 <sup>[12]</sup>
Female:male	0.92	Usually > 1 <sup>[1]</sup>
Adenoma	18.75%	33-80% <sup>[1]</sup>
Myelolipoma	33.33%	7-15% <sup>[8,13,14]</sup>
Pheochromocytoma	20.83%	2-20% <sup>[1]</sup>
Low HU on CT in pheochromocytoma (<10)	2 out of 10 (20%)	2 out of 374 <sup>[15]</sup>
Normotensive pheochromocytoma	2 out of 10 (20%)	10-40% <sup>[16]</sup>
Bilateral masses	12.5%	10-15% <sup>[17,18]</sup>

with incidentaloma or having familial screening, where the tumor may be smaller and less functionally active at presentation.<sup>[20]</sup> In the present study, two out of 10 patients were normotensive (20%).

Larger studies have shown that only 0.5% of pheochromocytomas have an unenhanced CT attenuation of  $\leq 10$  HU.<sup>[21-23]</sup> In a review by Buitenwerf *et al.*,<sup>[22]</sup> the CT images of 222 histologically proven pheochromocytomas revealed that only a single tumor had an unenhanced attenuation of  $< 10$  HU. In a study by Canu *et al.*,<sup>[15]</sup> two (0.5%) of 376 histologically proven pheochromocytomas had an unenhanced CT attenuation value of exactly 10 HU and 99.5% ( $n = 374$ ) were with HU  $> 10$ . Despite the retrospective design of these studies, unenhanced attenuation on a CT scan is considered a valuable tool to distinguish lipid-poor adenomas from pheochromocytomas. On the contrary, there lies the inherent risk of a missed diagnosis, prolonged exposure to catecholamines, and increased cardiovascular morbidity and mortality.<sup>[24,25]</sup> It has been suggested that in the presence of additional pointers such as elderly patients, heterogeneity, or evidence of tumor necrosis, patients should be considered for the biochemical testing for pheochromocytoma, even with an unenhanced CT attenuation of  $< 10$  HU.<sup>[1]</sup> Biochemical testing for pheochromocytoma has an excellent negative predictive value of 0.99.

However, in the present study, two out of 10 patients with biochemical and biopsy-proven pheochromocytoma had a CT attenuation value  $< 10$  HU. These patients had elevated pre-operative urinary metanephrine levels; one was reported as myelolipoma, and one was reported as adenoma on a non-contrast CT scan. This underscores the importance of biochemical evaluation for catecholamine excess in patients with incidentaloma.

Autonomous cortisol secretion (ACS) is associated with increased prevalence of morbidities such as hypertension,<sup>[26]</sup> insulin resistance,<sup>[27]</sup> type 2 diabetes mellitus,<sup>[28]</sup> obesity,<sup>[29]</sup> metabolic syndrome,<sup>[30]</sup> and increased mortality.<sup>[31]</sup> ACS has emerged as the one most common functional abnormality in patients with AI with prevalence rates of up to 20%.<sup>[32,33]</sup> In the present study, 14.5% patients were found to have possible autonomous or autonomous cortisol secretion.

We have reported two patients with ACS and two patients with possible ACS among biopsy-proven cases of myelolipoma. There have been similar case reports suggestive of ACS in adrenal myelolipoma as well as Cushing syndrome associated with myelolipoma.<sup>[34-36]</sup> The proposed mechanism is myelolipoma admixed with the hormone-secreting adenoma tissue. There are scarce data regarding the long-term outcome in such patients; usually, the long-term prognosis is good, similar to cortisol-producing adenomas, with resolution of Cushing features and no recurrence following re-section.<sup>[36]</sup>

Adrenal insufficiency is not a common feature of AI. In our study, one patient with a unilateral mass had adrenal insufficiency subsequently diagnosed as sickle cell anemia with extramedullary erythropoiesis. In the present study, two patients with incidentaloma were found to have extramedullary erythropoiesis.

Extramedullary erythropoiesis affecting adrenal glands is uncommon as per the literature, which could arise probably because of the compensatory physiological mechanism in cases of altered medullary hematopoiesis. This could be seen in hemoglobinopathies, leukemia, lymphoma, and myelofibrosis.<sup>[37]</sup> In rare cases, bilateral adrenal metastases can lead to adrenal insufficiency. Thus, it has been recommended that in all patients with potentially bilateral metastases, adrenal insufficiency should be considered and clinically evaluated.<sup>[1]</sup>

Since hemoglobinopathies are more commonly seen in this part of the country,<sup>[38]</sup> a higher degree of suspicion and appropriate screening for adrenal insufficiency should be considered in patients depending on the clinical scenario.

In various studies, the mean diameter of AI discovered by CT scan is 3 cm, ranging from 0.8 to 23 cm.<sup>[19,39-41]</sup> In the present study, the mean diameter of incidentaloma on CT scan was 6.21 cm. In another study conducted in an endocrine surgery department in a tertiary care centre in India, the mean diameter of incidentaloma was found to be 7.5 cm.<sup>[42]</sup> This could be because of the relatively delayed presentation and imaging.

There is a correlation between tumor size and risk of adrenocortical cancer: 2% risk in AIs  $< 4$  cm, 6% in AIs between 4.1 and 6 cm, and 25% in AIs  $> 6$  cm.<sup>[43]</sup> A large Italian study of patients with AI ( $n = 887$ ) reported that 90% of adrenocortical carcinomas had a diameter of  $> 4$  cm at presentation, and a 4 cm cut-off had a 93% sensitivity for detecting adrenocortical carcinoma.<sup>[32,44]</sup> Our study also corroborates with this statement as all the patients with ACC had a size of AI  $> 4$  cm.

In various studies, majority of AIs are unilateral; however, bilateral AIs may be found in 10–15% of the cases, and the most common causes of bilateral AIs were metastasis, primary bilateral macronodular adrenal hyperplasia (PBMAH), and bilateral cortical adenomas in large studies.<sup>[17,18]</sup> In the present study, bilateral masses were found in 12.5% patients, and the causes were myelolipoma, lymphoma, and adenoma.

**Table 4: Imaging discrepancy from final diagnosis**

No of cases	Probable imaging diagnosis	Final diagnosis
1	Myelolipoma	Pheochromocytoma
1	ACC	Extramedullary erythropoiesis
1	Adenoma	Pheochromocytoma

Our study has shown that relying solely on the imaging characteristic of AI for the diagnosis and management could have led to potentially serious adverse events in at least three patients. The comparison of probable imaging diagnosis and diagnosis established on biochemical evaluation and biopsy results is shown in Table 4.

The limitations of the present study include retrospective design of the study, with no inclusion of contrast imaging data and follow-up data. Since majority of the patients underwent non-contrast enhanced CT scan in the first sitting, they were not subjected to contrast study as it was not felt necessary for further management. This was decided based on the suggestion by the ESE and ENSAT guidelines. Long-term follow-up data were limited due to loss of follow-up of patients. A prospective study would add more value to our findings.

## CONCLUSION

Our study has highlighted certain rare but important characteristics of AI. We encountered discrepancy between non-contrast CT diagnosis and functional status of AI, which signifies the need for pre-operative biochemical evaluation for pheochromocytoma. We also described a case with extramedullary erythropoiesis presenting as AI and adrenal insufficiency. Apart from the routine biochemical and imaging evaluation, specific evaluation for such rare possibilities should be considered in AI cases as per the clinical scenario. AI indeed can deceive the unwary!

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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