ENDOCRINOLOGY

Adrenal incidentalomas: clinical, biological, imaging and therapeutic features

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Abstract

Background. Adrenal incidentaloma is an adrenal mass discovered incidentally during an imaging examination that was not conducted to investigate an adrenal pathology. Its etiologies are varied, which determines the choice of different therapeutic options. The objective of our study is to describe the clinical, biological, etiological, and therapeutic aspects of adrenal incidentalomas in our series.

Methods. This is a retrospective study including 55 patients who were managed for adrenal incidentalomas. Demographic characteristics, clinical evaluations, imaging features, and functional status were analyzed.

Results. The mean age was 55.49 ± 13.53 years with a female predominance (65.4%). The circumstances of discovery were predominantly digestive (54.5%). Computed tomography (CT) was the most frequent imaging method used in the first detection of adrenal incindentalomas. These adrenal masses were unilateral in 72.8% of patients, and bilateral in 27.2% of cases. Their sizes ranged from 10 to 135 mm. In terms of secretory profile, the etiologies of adrenal incidentalomas were predominantly non-functional, followed by pheochromocytomas, and hypercortisolism, then primary hyperaldosteronism. Adrenalectomy was indicated for 23.6% of our patients.

Conclusion. Our results are in agreement with those in the literature, showing that patients with an incidental adrenal mass need a multidisciplinary approach involving clinical and biological screening for endocrine hypersecretion, as well as radiological evaluation to ensure an effective etiological diagnosis and to establish a personalized and optimal therapeutic management plan.

Keywords: adrenal incidentalomas, computed tomography, pheochromocytoma, hypercortisolism, primary hyperaldosteronism, adrenalectomy

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Introduction

Adrenal incidentaloma (AI) is an adrenal mass that is identified incidentally during an imaging study conducted for an unrelated reason [1]. Masses discovered during the staging of a malignant disease and thought to be metastatic are not considered incidentalomas [2]. The majority of adrenal incidentalomas are benign and non-functional. The evaluation of whether they are malignant and/or functional constitutes the basis of the clinical approach [3,4]. Their incidence is constantly increasing due to the improved performance of imaging techniques and the widespread use of these diagnostic indications [1,2,3]. The prevalence of adrenal masses depends on the size chosen as the pathogenicity threshold, and on the nature of the radiological examination used. It appears justified to consider only tumors with a major axis of 1 cm or more, as smaller lesions are unlikely to correspond to deleterious entities [5–8]. The main issues established by the

discovery of an adrenal incidentaloma are the indications for surgical excision, and the modalities of monitoring if surgery is not indicated.

There are several guidelines for managing patients with adrenal incidentalomas, but the significant heterogeneity among patients makes it challenging to establish an optimal approach, especially for radiological follow-up, therefore it is crucial to gather more detailed information related to adrenal incidentaloma cases to develop more reliable management guidelines. Furthermore, their management must be the subject of a multidisciplinary meeting, involving several specialties for an optimal therapeutic decision, adapted and personalized for each patient [4,6,9,10]. The aim of our study is to determine the clinical, paraclinical, etiological and therapeutic management of patients with adrenal incidentalomas.

Methods

Study design

This is a retrospective descriptive study running for eight years, from January 2015 to December 2023, and was conducted at the Endocrinology-Diabetes-Nutrition Department of a university hospital center.

Sample size

The study included 55 patients hospitalized for the investigation of adrenal incidentaloma at the Endocrinology-Diabetology-Nutrition Department.

Inclusion criteria

- Patients undergoing investigation for incidentally discovered adrenal masses.
- Complete medical records including clinical observations, biochemical analyses, and radiological assessments.

Exclusion criteria

- Incomplete medical records.
- Adrenal masses discovered during an abdominal imaging examination motivated by the exploration of an adrenal pathology.

Data collection

Demographic, clinical, and paraclinical data were collected from the patients including age, sex, personal history of neoplasia, family and/or personal history of endocrine diseases, history of infectious episodes, trauma or recent abdominal surgery, previous treatments intake (aspirin, anti-coagulants), recent weight loss, altered general condition. Any history of hypertension or diabetes mellitus, and circumstances in which the adrenal incidentaloma was discovered. All patients in our series underwent an exhaustive clinical examination, which included assessments of blood pressure and pulse, screening for clinical signs of inappropriate hormone secretion, examination of the thyroid, liver, spleen, breasts and lymph node regions to identify potential neoplasms.

The hormonal evaluation of our patients included the assessment of 24-hour urinary methoxylate levels using liquid chromatography-mass spectrometry. This included measuring 24-hour urinary normetanephrines (normal range: 0.40 to 2.10 µmol/24h) and 24-hour urinary metanephrines (normal range: 0.20 to 1.00 µmol/24 h). Patients with 24-hour urine metanephrine and/or normetanephrine levels more than 3-folds higher than the normal value were classified as pheochromacytoma [10]. Overnight dexamethasone suppression test (DST) was found elevated when morning cortisol levels are below 18 ng/ml, in cases where post-DST cortisol levels exceeded 18 ng/ml, a 2-day, 2 mg DST was conducted, involving the administration of 0.5 mg oral dexamethasone every 6 hours for 48 hours [11,12]. The subclinical hypercortisolism or renamed currently in the new consensus "mild autonomous cortisol secretion" (MACS) was identified in patients with adrenal adenomas, with the absence of clinical manifestations of Cushing's syndrome, when post-dexamethasone suppression test (DST) cortisol levels were ≥18 ng/ml [13]. In these cases, screening for cortisol-related comorbidities, including hypertension, diabetes, dyslipidemia, and osteoporosis, should be performed [13]. For late night salivary cortisol, the cut-off value was set as 2.7 ng/ml [14]. Primary hyperaldosteronism was screened in hypertensive patients and/or those with hypokalemia by measuring aldosterone and renin levels. The aldosterone/plasma renin ratio was then calculated after confirming assay conditions. The diagnosis was confirmed if aldosterone levels exceeded 550 pmol/L with an aldosterone/renin ratio exceeding 64 [13]. In the case of bilateral adrenal incidentalomas, it is recommended to systematically screen for adrenal insufficiency and to exclude a 21-hydroxylase enzymatic deficiency by measuring the 17-hydroxyprogesterone level following stimulation with a Synacthen test (normal value <10 ng/mL) [15].

Radiological evaluation is a crucial step in the etiological diagnosis of adrenal masses. It included CT scan, abdominal ultrasound and MRI depending on the patient's context, with the aim of determining the nature of the lesion by specifying the radiological characteristics of the mass. After determining the etiological diagnosis from the clinical and paraclinical data, the decision to proceed with either therapeutic abstinence or surgical intervention was guided by an assessment of the mass's secretory characteristics and radiological features. Ultimately, we gathered and evaluated the pathological results for the patients who had undergone surgical interventions, along with monitoring their subsequent clinical progress.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS) version 21(IBM, Armonk, NY), descriptive statistical analyses were conducted as follows:

- Headcounts and percentages were calculated for qualitative variables.
- Measures of central tendency (mean and median) and measures of dispersion (standard deviation) were computed for quantitative variables.

Ethics

The ethical review committee at the Faculty of Medicine, Mohammed 1st University of Oujda (CERBO) approved the study design and protocol, and the study design has been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki. Considering the retrospective type of the study, we worked on clinical records, and all involved patients provided oral consent to the use of their medical data.

Results

We enrolled 55 patients in our study, including 36 women (65.4%) and 19 men (34.5%), with a sex ratio (F/M) of 1.8. The mean age of patients was 55.50 ± 13.53 years, ranging from 22 to 80 years. Regarding the personal medical history of our patients; 49.6% had arterial hypertension, 27.6% were diabetic, 11% had dysthyroidism, 1.8% had a history of tuberculosis, and 10% had a neoplasia.

The discovery symptoms were dominated by digestive pathologies in 54.5% of patients, followed by urological diseases in 30.9%, cardiac pathologies in 5.5%, then gynecological and pulmonary conditions in 5.5% and 3.6% of patients, respectively. Adrenal CT scan was the most common paraclinical examination of discovering the adrenal mass in 87.2% of cases, followed by abdominal ultrasound in 11%, then abdominal MRI in 1.8%.

Adrenal masses were found unilaterally in 72.8% of cases, predominantly on the left side (40% left versus 32.8% right), and bilaterally in only 27.2% of cases. The mass size was less than 4 cm in 85.5% of cases while in 14.5% of cases it exceeded this threshold. Regarding spontaneous density, 67.2% of cases had a value below 10 Hounsfield Units (HU), whereas 32.8% had a density over 10 HU (Table I).

The clinical examination revealed arterial hypertension in 49.6% of patients, clinical Cushing's syndrome in 7.2%, while no symptoms of virilization or adrenal insufficiency were observed in any of our patients.

The hormonal exploration had shown that the urinary methoxyl derivatives were positive in 18.1% of cases. Regarding steroid assessment, a minute suppression test revealed that cortisol level at 8 a.m. was above 18 ng/ml in 12.7% of our patients after the test, free urinary cortisol was elevated in 1.8% of cases, and the salivary cortisol levels were elevated in 3.6% of our patients. All of our patients had their potassium levels checked; 3.6% of cases had hypokalemia, the analysis of the Aldosterone/Renin Ratio revealed primary hyper aldosteronism in 9% of cases. Moreover, the androgen hypersecretion was found in 1.8% of our cases and the 17-hydroxy-progesterone was measured in 8 patients with bilateral adrenal incidentalomas showing normal results. Additionally, adrenal insufficiency was excluded in these patients.

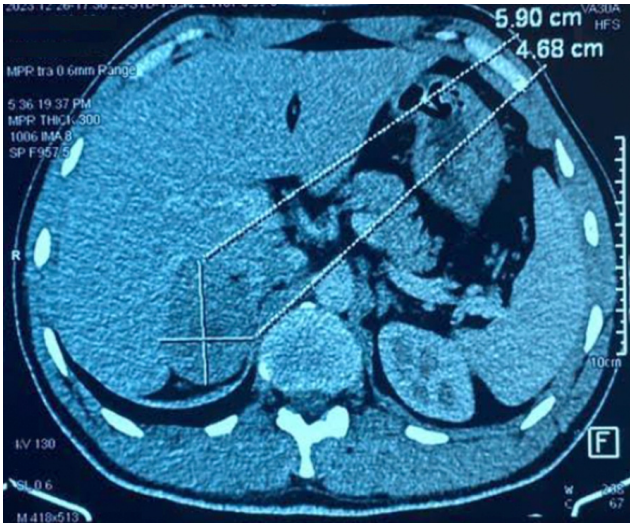

Figure 1. Adrenal CT scan reveals a right adrenal incidentaloma evoking pheochromocytoma (the lesion measures 59 mm along the long axis, with a spontaneous density exceeding 10 UH, an absolute washout of 34%, and a relative washout of 24%).

The etiological investigation revealed that 61.9% of our patients had non-functional adrenal masses, while 38.1% had secreting masses. Among the functional cases, pheochromocytoma accounted for 18.1%, primary hyperaldosteronism for 9%, and hypercortisolism for 12.7%, with subclinical hypercortisolism present in 9% of cases. Screening for comorbidities in patients with subclinical hypercortisolism revealed obesity in 20%, hypertension in 40%, and diabetes in 20% of cases.

Table I. Imaging characteristics of adrenal masses.

Lateralization	Left adrenal [n, (%)]	22 (40%)
	Right adrenal [n, (%)]	18 (32.8%)
	Bilateral [n, (%)]	15 (27.2%)
Longest diameter (mm)		30,76 (10-135)
The dimensions of adrenal masses classified into 3 categories	< 4 cm	83,6%
	4-6 cm	7,4%
	> 6 cm	9%

n: number, %: percentage

Regarding therapeutic management, after a multidisciplinary meeting the surgical intervention was indicated in 23.6% of our patients (13 cases) and the anatomopathological study confirmed the diagnosis of pheochromocytoma in 10 patients (18.1%), the adrenocortical carcinoma, angiomatous endothelial cyst, and adrenocortical adenoma each occurred in one patient (1.8%). The post-operative outcome was favorable for all patients who underwent surgery. Additionally, in those patients for whom therapeutic abstention was deemed appropriate, follow-up evaluations indicated that their CT scans remained stable, and no additional secretion was detected.

Discussion

In our study, the majority of patients were female, accounting for 65.4% of the cases, with a mean age of 55.49 ± 13.53 years. The most commonly reported initial symptoms were gastrointestinal, affecting 54.5% of the patients. Computed tomography (CT) was the predominant imaging technique employed for the initial identification of adrenal incidentalomas. These adrenal masses were found to be unilateral in 72.8% of cases, with a left-sided prevalence of 40% and right-sided involvement in 32.8%. Bilateral cases were observed in 27.2%. Their sizes ranged from 10 to 135 mm, with a median of 30.76 mm. The endocrine evaluation revealed that a non-functioning adrenal adenoma was predominant in 61.9% of cases, a pheochromocytoma was found in 18.1%, hypercortisolism in 12.7%, and primary hyperaldosteronism in 9% of cases.

The prevalence of adrenal incidentalomas varies according to the patient's environmental context during exploration [16].In radiological studies, the prevalence varied between 0.3% and 4.4% among patients undergoing abdominal CT scan [8,17,18].

In our study, the age range was wide, spanning from 22 to 80 years, with a median age of 55.5 years, this finding aligns with existing literature. For instance, N. Tutuncu et al [19] reported a median age of 50.9 years (range: 23–79) in their study of 33 adrenal incidentaloma cases. Similarly, N. Yilmaz et al [20] in a larger study, including 755 cases, reported an average age of 56 years (range: 18–86). Thus, our research, aligns with existing literature, demonstrating that a predominant proportion of patients with adrenal incidentalomas are female. In particular, A. Comlecki et al [12] reported a female-to-male ratio of 2.41 in their study of 293 cases, whereas F. Mantero et al [21] in their multicenter analysis involving 1,004 cases, observed a sex ratio (F/M) of 1.39. These results may be attributed to the elevated incidence of biliary and gynecological disorders among women, necessitating thorough radiological investigations [15].

Moreover, the majority of our patients (61.8%) were overweight, hypertension was diagnosed in 49.6% of cases, and diabetes in 27.6%. These results align with numerous studies indicating a rising prevalence of adrenal incidentalomas correlated with advancing age and the presence of comorbidities, including hypertension, diabetes mellitus, and obesity [16,7,17,18].

The circumstances of discovery of adrenal masses in the literature exhibit significant variability, as summarized in Table II. These cases are frequently associated with digestive disorders, which constituted 54.5% in our series. Similarly, in the study by N. Yilmaz et al, digestive symptomatology was predominant, accounting for 39.6% of cases. In contrast, in the study by A. Comlecki et al, the predominant symptoms were non-specific, representing 24% [12,20].

Table II. The variability of the circumstances of discovery of adrenal incidentalomas.

	Digestive	Urological	Cardiac	Gynecological	Pulmonary	Nonspecific symptoms
Our series	54.5%	30.9%	5.5%	5.5%	3.6%	-
Series of N. Yilmaz et al [20]	39.6%	20.4%	-	13.2%	20.4%	26.8%
Series of A. Comlekciet al [12]	20%	-	11%	-	15%	24%

Table III. The lateral distribution of adrenal masses across various studies.

	Our series	Y. Hamid et al [24]	N. Yilmaz et al [20]	N. Hiroi et al [25]	S. Bovioet al [26]	L. Li et al [1]
Unilateral	72.8%	100%	86%	92.9%	86.8%	92.4%
Left adrenal	40%	58.3%	49.7%	42.9%	60.8%	46.9%
Right adrenal	32.8%	41.7%	36.3%	50%	26%	45.4%
Bilateral	27.2%	0%	14%	7.1%	13.2%	7.6%

Computed tomography (CT) of the adrenal glands was the most frequently used paraclinical tool for detecting adrenal masses in our study, employed in 87.2% of cases. This aligns with the findings of N. Yilmaz et al, who analyzed a series of 755 patients and reported CT use in 82% of cases [20]. Our investigation, along with other studies detailed in Table 3, demonstrates that adrenal masses are more frequently observed on the left side. However, some studies indicate a right-sided predominance in 50-60% of cases. This variation may be attributed to the fact that many of these studies used ultrasonography, which is typically less effective in identifying masses on the left side [20–23].

The recent consensus on the management of adrenal incidentalomas identifies spontaneous density as the crucial parameter for determining the type of tumor. In fact, if the adrenal mass has a spontaneous density of less than 10 UH, it can be considered benign regardless of its size [27]. Conversely, if the spontaneous density is greater than 10 UH, it is important to analyze the size of the mass. It has been shown that the risk of malignancy increased significantly in lesions larger than 40 mm [11,28]. In our series, 16.4% of cases involved adrenal masses greater than 40 mm, including one malignant adrenocortical tumor measuring 72 mm that was adherent to hepatic segments VI and VII. Additionally, the median size of adrenal masses in our study was 30.76 mm. These findings align with those documented in the literature, including the study by Osella et al, which reported a median size of 30 mm [2]. Based on the literature, the proportion of cancers is less than 2% for masses smaller than 40 mm, 6% for those between 40 and 60 mm, and greater than 25% for masses larger than 60 mm [29].

Nevertheless, this size criterion has inherent limitations, as malignant tumors can present with smaller dimensions. In fact, 75% of metastatic tumors are smaller than 40 mm [8]. In addition, the progression of tumor size is critical; a tumor is classified as progressive and consequently at a higher risk of malignancy if it grows by 10 mm within a one-year period [6].

Among our patients, the spontaneous density was greater than 10 UH in the patient diagnosed with adrenocortical carcinoma, as well as in the majority of cases of pheochromocytoma (8 of 10 cases), the other two patients with pheochromocytomas had tumors larger than 4 cm. This finding is consistent with the recent European consensus on the evaluation and management of adrenal incidentalomas, which underscores the critical importance of assessing urinary and plasma metanephrines for any lesion demonstrating a spontaneous density greater than 10 UH [27].

After radiologic evaluation of adrenal masses, an exhaustive endocrine assessment is imperative to ascertain their secretory activity and to detect lesions that may require surgical intervention. This evaluation should systematically include screening for glucocorticoid and catecholamine hypersecretion, given that the mortality rate associated with undiagnosed pheochromocytomas is notably high, with as many as 80% of patients succumbing to complications during surgical procedures or anesthesia [8].

Among our cases, the majority of adrenal incidentalomas were non-functional (61.9%) , this is comparable to the prevalence reported in the literature, which ranges from 52.3% to 85% as detailed in Table 4 [1,12,20,30].

In the literature, the prevalence of functionality in adrenal incidentalomas exhibits considerable variability. In our study, 18.1% of patients demonstrated positive results from the urinary methoxylated derivatives assay, which is comparable to the findings of L. Li et al (11.6%) and falls within the reported prevalence range of 1.5% to 25% [1]. However, this observed percentage, is higher than that reported in other studies (Table IV) which may be explained by our strategy of systematic screening for methoxylated derivatives in patients with adrenal incidentalomas.

In addition, the cortisolic secretion of adrenal masses in our series was observed in 12.7% of patients, aligning with the prevalence reported in the literature, which ranges from 5% to 14% [31] . The assessment of cortisol related comorbidities in cases of subclinical hypercortisolism is a critical determinant in the therapeutic decision-making process, and surgical intervention may be indicated for patients with important comorbidities [27]. Furthermore, the elevated prevalence of primary hyperaldosteronism observed in our study (9%) compared to 1.6–4.3% reported in other investigations can be attributed to our targeted screening methodology. We specifically focused on patients with adrenal masses who presented with arterial hypertension and/or hypokalemia, as well as those with radiological findings indicative of a Conn adenoma. This approach has facilitated the identification of a significant number of subclinical aldosterone-producing tumors (Table IV).

The management of adrenal incidentalomas requires a multidisciplinary approach, guided by two major factors: signs of malignancy and the presence of hormonal hypersecretion [9].This approach was applied to 23.6% of our patients who underwent unilateral adrenalectomy. Conversely, patients with asymptomatic, non-functioning unilateral adenomas that display benign characteristics on imaging are recommended to pursue a conservative management strategy. This typically entails radiological surveillance at intervals that vary based on the size and density of the mass observed in initial imaging, in alignment with the recent guidelines from the French Society of Endocrinology regarding adrenal incidentalomas [27]. The anatomopathological analysis in our findings revealed pheochromocytoma in 18.1% of cases and adrenocortical carcinoma in 1.8% of cases. These results approve the reliability of imaging criteria for diagnosing malignancy and highlight the essential role of radiological characteristics in guiding treatment decisions.

Table IV. Secretory profile of adrenal masses in different series.

	AI non-functional	AI functional		
		Pheochromocytomas	Hypercortisolism	Primary hyperaldosteronism
Our series	61.9%	18.1%	12.7%	9%
A. Comleckiet al [12]	67.4%	5.3%	14.9%	4%
N. Yilmazet al[20]	71.8%	3.8%	15.8%	3.7%
F. Mantero et al [21]	85%	4.2%	9.2%	1.6%
L. Li et al [1]	72.6%	11.6%	7.8%	4.3%
T. Ichijo et al [30]	52.3%	7.9%	7.9%	4,1%

AI: Adrenal incidentalomas

This study has some limitations; firstly, it is a retrospective study, based on the experience of a single establishment, and consequently there is a lack of information on other interesting parameters; secondly, the small sample size represents another constraint on our study.

Conclusions

Adrenal incidentalomas are becoming increasingly frequent due to advancements in medical imaging techniques. Our series of fifty-five patients has described and highlighted the clinical and paraclinical features to determine the etiological diagnosis for these patients. It is crucial to conduct screening for clinical manifestations of hypersecretion, in conjunction with performing biological assays to identify pheochromocytoma, subclinical hypercortisolism, and primary hyperaldosteronism. Moreover, morphological assessment, predominantly by CT imaging, is essential for the detection of malignancy. These elements should be used to guide the therapeutic decision, whether it be adrenalectomy or conservative management, this decision should be made in the context of a multidisciplinary meeting involving the endocrinologist, surgeon, radiologist, and nuclear medicine physician to ensure the most optimal and patient specific approach.

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