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A Decade of Insights into Bilateral Adrenal Masses: Epidemiology, Clinical Profiles, And Therapeutic Approaches

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Abstract

Bilateral adrenal masses (BAMs) are rare, accounting for 10-15% of adrenal masses. Their diagnostic and therapeutic approaches differ from those of unilateral masses. This study aimed to analyze the epidemiological, clinical, paraclinical, and therapeutic profiles of BAMs. It is based on a retrospective analysis of 30 patient records from the Endocrinology, Diabetology, and Nutrition Department at CHU Hassan II in Fez, over a 12-year period.

The average age of the patients was 53 years, with a male predominance (53.3%). BAMs were symptomatically revealed in 46.7% of cases, incidentally discovered in 23.3%, identified during tumor staging in 20%, and associated with a genetic syndrome in 10% of cases. Clinical examination revealed hypertension in 23.3% of patients, an abdominal mass in 10%, signs of adrenal insufficiency in 10%, hypercortisolism in 6.67%, and hyperandrogenism in 16% of cases.

Biological assessment showed elevated urinary or plasma metanephrine derivatives in 9 patients, hypercortisolism in 3 patients, adrenal insufficiency in 3 patients, 11-β-hydroxylase enzyme block in 3 patients, and primary hyperaldosteronism in 1 patient. Adrenal computed tomography (CT) was performed in 29 patients. A staging workup, including PET scan, was requested in 20% of cases. MIBG scintigraphy was performed in 23.3% of patients.

The investigations revealed 53% of BAMs were secreting and 47% non-secreting. There were 9 cases of pheochromocytomas, including 5 associated with a syndrome (3 MEN2a, 1 MEN2b, 1 VHL), 8 cases of non-secreting adenomas, 3 cases of congenital adrenal hyperplasia due to 11-β-hydroxylase enzyme block, 2 cases of adrenal metastases, 2 cases of adrenocortical carcinoma, 2 cases of adrenal cysts, 1 case of Conn's adenoma, 1 case of cortisol-secreting adenoma, 1 case of primary adrenal lymphoma, and 1 case of adrenal hematoma.

Treatment included the management of emergencies and preoperative preparation for patients eligible for surgery. Bilateral adrenalectomy was performed in 33.3% of patients, and unilateral adenectomy in 1 case of cortisol-secreting adenoma. Medical treatment was initiated in 16.6% of cases, and palliative treatment in 13.33% of cases. Surveillance alone was implemented in the remaining 33.3%. Prognosis depends on the type of adrenal mass, with outcomes marked by the death of one case of malignant adrenocortical carcinoma and one case of primary adrenal lymphoma.

Our study, involving 30 cases of BAMs, highlights their clinical, biological, radiological, therapeutic,

and prognostic characteristics. Data in the literature are limited compared to unilateral adrenal masses. Future larger studies are desirable for optimal management.

Keywords: Bilateral Adrenal Incidentalomas, Adrenal Insufficiency, Hormonal Assessment, Adrenal CT Scan, Genetic Study

Introduction

Bilateral adrenal masses (BAMs) encompass a variety of pathologies that can be either adrenocortical or adrenal medullary, secreting or non-secreting, benign or malignant. Although these tumors are rare, their incidence is increasing due to advances in imaging techniques. BAMs present with a wide range of clinical manifestations, from asymptomatic incidental findings to severe clinical presentations, with diverse etiologies. Their diagnostic management relies on clinical assessment, biological and radiological investigations, and histopathological examination of biopsied or surgically removed cases. Treatment primarily depends on the secretory profile, tumor size, signs of malignancy, and associated comorbidities.

Our objective, through a retrospective study conducted in the Endocrinology, Diabetology, and Nutrition Department at CHU Hassan II in Fez, was to examine the clinical, biochemical, and radiological characteristics and management outcomes in our patients with BAMs.

Materials and Methods

I. Study Materials

a. Type

This is a retrospective and descriptive study based on a review of clinical records of patients followed in the Endocrinology, Diabetology, Metabolic Diseases, and Nutrition Department at CHU Hassan II in Fez.

b. Duration and Location of the Study

The study covered a 12-year period at the Hassan II University Hospital in Fez.

c. Study Population

- Inclusion Criteria: Patients followed for BAMs with complete medical records.
- Exclusion Criteria: Patients with incomplete records or lost to follow-up.

II. Methods

Information was collected using data sheets detailing the epidemiological, clinical, paraclinical, therapeutic, and follow-up data of the patients.

III. Statistical Analysis

Statistical analysis was performed using SPSS version 25, employing descriptive analyses such as sums, percentages, means, and extremes

Results

1. Epidemiological Data

We studied 30 patients with BAMs. The average age was 53 years (standard deviation: 14.2 years). A slight male predominance was observed (53.33%), with a female-to-male ratio of 1.14.

2. Clinical Data

- Medical History: MEN2A (6.67%), Von Hippel Lindau syndrome (3.33%), pulmonary tuberculosis

(3.33%), anticoagulation (3.33%).

- Modes of Discovery:
  - Symptomatic (46.7%)
  - Incidental discovery (23.3%)
  - Genetic syndrome (20%)
  - Tumor staging (20%)
- Clinical Signs: underweight (10%), abdominal mass (10%), acute adrenal insufficiency (10%), hypercortisolism (10%), hyperandrogenism (16%), goiter (20%), gynecomastia (3.33%), neoplasia (35%), tongue and lip schwannoma (3.33%).

3. Biological Data

- Non-Specific Findings: Hypokalemia (10%), hyperglycemia (30%), chronic renal failure (6.67%).
- Specific Findings:
  - Peripheral adrenal insufficiency (10%)
  - Positive urinary or plasma metanephrine derivatives (30%)
  - Biochemical Cushing's syndrome (10%)
  - Primary hyperaldosteronism (3.33%)
  - Hyperandrogenism (6.66%)
  - Genetic forms: MEN2a (10%), MEN2b (3.33%), VHL syndrome (3.33%)
  - Congenital adrenal hyperplasia (10%)

4. Radiological and Functional Data

- Abdominal Ultrasound (20% of patients admitted to the department had an abdominal ultrasound): Bilateral adrenal cyst (6.67%), bilateral pheochromocytoma (6.67%).
- Abdominal CT Scan (96.6% of cases):
  - Average tumor size: 24.6 mm ± 11.7 mm (right), 23.2 mm ± 11.1 mm (left)
  - Spontaneous density < 10 HU (70%), > 10 HU (26.67%)
  - Absolute washout < 60% (26.67%), > 60% (20%)
  - Relative washout < 40% (26.67%), > 40% (20%)
  - Signs of malignancy (20%)
- Abdominal MRI: Adenoma (1 patient), bilateral pheochromocytoma (1 patient).
- CT-TAP:
  - Splenic nodular lesions, rectosigmoid wall thickening in the patient followed for bronchial carcinoma.
  - Inferior vena cava invasion in the first patient with adrenocortical carcinoma.
- MIBG Scintigraphy: Bilateral adrenal uptake (7 cases of pheochromocytoma).
- PET-CT: Hepatic metastases, peri-aortic-caval lymph nodes, inferior vena cava invasion (1 case of malignant adrenocortical carcinoma).

5. Adrenal Biopsy

Performed before admission to the department in 6.67% of patients:

- B-cell non-Hodgkin lymphoma (1 patient)
- Malignant adrenocortical carcinoma (1 patient)

6. Final Diagnosis

Répartition des diagnostics (Tableau 1) :

Type of BAM	Number of Cases	Percentage
Pheochromocytoma	9	30%
Non-secreting adenoma	8	26.67%
Adrenal metastases	2	6.67%
Adrenal hyperplasia	3	10%
Adrenal cyst	2	6.67%
Adrenocortical carcinoma	2	6.67%
Cortisol-secreting adenoma	1	3.33%
Conn's adenoma	1	3.33%
Primary adrenal lymphoma	1	3.33%
Adrenal hematoma	1	3.33%

7. Therapeutic Management

- Emergency Management: Acute adrenal insufficiency, hypertensive crisis, hypokalemia.
- Surgical Treatment (11 patients):
  - Pheochromocytoma (9 cases)
  - Adrenocortical carcinoma (1 case)
  - Cortisol-secreting adenoma (1 case)
- Non-Surgical Treatment with Follow-Up (19 patients):
  - Non-secreting adrenal adenoma (8 cases)
  - Adrenal hyperplasia (3 cases)
  - Adrenal metastases (2 cases)
  - Adrenal cysts (2 cases)
  - Conn's adenoma (1 case)
  - Metastatic adrenocortical carcinoma (1 case)
  - Adrenal lymphoma (1 case)
  - Adrenal hematoma (1 case)

8. Histhopathological Data

- Pheochromocytoma (81% of operated cases)
- Adrenocortical carcinoma (3.33%)
- Cortisol-secreting adenoma (3.33%)

9. Evolutionary Data

- Appropriate follow-up of operated cases with good outcomes.
- Adapted surveillance of non-operated cases, with two deaths: metastatic malignant adrenocortical carcinoma and bilateral primary adrenal lymphoma.

Discussion

I. Epidemiological Study of Bilateral Adrenal Masses (BAMs)

1. Prevalence

Bilateral adrenal masses are rare, with a prevalence ranging from 0.3% to 0.6% in the general population [1,2] . They account for 10-15% of adrenal incidentalomas [3].

2. Average Age

The average age at diagnosis of BAMs in our study was 53 years, which aligns with findings from other studies, such as J. Zhou's study (53.1 years) [4] and N. Lomte's study (55.8 years) [5] .

3. Sex Distribution

There was a male predominance in our study, consistent with the literature [4,5].

II. Etiological Diagnosis

The following table presents a comparative overview of the findings from our series and those from studies by Zhou et al. and Lomte et al. [4,5] (table 2):

Series	Location	Duration	Number of Cases	Type	Nb	%
Zhou et al.	China	2002-2007	18 cases	Pheochromocytoma	06	33.33%
				Non-secreting adenoma	04	22.22%
				Metastasis	02	11.1%
				Lymphoma	04	22.22%
				Hyperplasia	01	5.55%
Lomte et al.	India	2001-2018	70 cases	Pheochromocytoma	28	40%
				Non-secreting adenoma	03	4.2%
				Metastasis	04	5.7%
				Lymphoma	07	10%
				Hyperplasia	03	4.28%
				Cyst	01	1.42%
Our series	Fez	2009-2021	30 cases	Pheochromocytoma	09	30%
				Non-secreting adenoma	08	26.67%
				Metastasis	02	6.67%
				Lymphoma	01	3.33%
				Hyperplasia	03	10%
				Cyst	02	6.67%

Other Types of BAMs : Bilateral adrenal myelolipoma [6] bilateral adrenal tuberculosis [7] and adrenal amyloidosis [8] are rare, with no cases found in our series.

This discussion highlights the rarity and diverse etiologies of bilateral adrenal masses, stressing the importance of comprehensive diagnostic evaluations to guide appropriate management.

III. Therapeutic Management of Bilateral Adrenal Masses (BAMs)

Management of BAMs primarily depends on radiological features and hormonal evaluation, guiding either surgical excision or conservative treatment with regular monitoring.

1. Management of Secreting BAMs

- **Bilateral Pheochromocytoma (BP):** Bilateral adrenalectomy is generally recommended, although partial resection may be considered for genetic syndromes like VHL and MEN2A [9].. Adjuvant therapy is planned for malignant pheochromocytomas [10].. In our series, all nine cases of BP underwent bilateral adrenalectomy following appropriate preoperative preparation.
- **Bilateral Cortical Adrenocortical Carcinoma:** Bilateral adrenalectomy via laparotomy is the standard treatment. If surgery is not possible, high-dose steroidogenesis inhibitors are used [11], with other palliative options available. In our series, one patient underwent laparotomy, while the metastatic case was referred to oncology.
- **Bilateral Cortisol-Secreting Adenoma:** Adrenalectomy is often considered after medical preparation, including steroidogenesis inhibitors and correction of Cushing's syndrome-related disorders [12]. The choice between unilateral or bilateral adrenalectomy remains debated [13,14,15].. In our series, one patient had a unilateral adrenalectomy laparoscopically after appropriate preoperative preparation.
- **Bilateral Conn's Adenoma:** Mineralocorticoid receptor antagonists are the treatment of choice according to the literature [8]. In our series, the patient was treated with spironolactone.
- **Congenital Adrenal Hyperplasia (CAH):** Hydrocortisone is essential for classic forms, while non-classic forms in adults generally do not require this treatment. Hyperandrogenism is usually managed with cyproterone acetate and 17β-estradiol [16].. In our series, patients with non-classic CAH received estrogen-progestin therapy.

2. Management of Non-Secreting BAMs

- **Non-Secreting Bilateral Adrenal Adenoma:** Management depends on size, nature, and evolution of the adenomas [17,18].. In our series, conservative management was adopted for benign adenomas smaller than 4 cm.
- **Bilateral Adrenal Metastases:** Treatment options include bilateral or partial adrenalectomy [19,20], with some cases also involving adjuvant or palliative care. In our series, both cases were managed by the oncology department.
- **Bilateral Adrenal Lymphoma:** Chemotherapy is the treatment of choice, with surgery rarely offering benefit [21].. In our series, the patient was referred to internal medicine for management after starting hydrocortisone therapy.
- **Bilateral Adrenal Cyst:** In the absence of hormonal secretion, management depends on size and cytological results [22,23,24]. Cysts larger than 6 cm require aspiration (with management based on the results), while those smaller than 6 cm are monitored. In our series, two patients with asymptomatic cysts less than 6 cm were followed without intervention.
- **Bilateral Adrenal Hematoma:** Medical treatment is usually sufficient, including analgesics, rest, and hydrocortisone if needed. Surgery is reserved for acute cases [25]. In our series, the patient did not develop any acute complications during follow-up.

This management exemplifies the challenge of adapting treatments to the individual characteristics of patients and the specific nature of their conditions.

IV. Follow-up and Prognosis

- Bilateral Pheochromocytoma: Lifelong follow-up is necessary due to the risk of late malignant recurrences and undiagnosed genetic syndromes [26]. Our series showed favorable outcomes with

regular monitoring.

- Bilateral Cortical Adrenal Carcinoma: Personalized follow-up, including clinical assessments and CT scans, is crucial [27,28]. Our cases demonstrated positive progression.
- Bilateral Conn's Adenoma: Gradual spacing of clinical and tomographic monitoring is recommended [29]. The patient in our series showed stabilized blood pressure and potassium levels with lifelong treatment.
- Bilateral Cortisol-Secreting Adenoma: Lifelong monitoring is needed due to the recurrence risk, though remission is common post-surgery [14]. No recurrences were observed in our series.
- Congenital Adrenal Hyperplasia: Regular follow-up is essential to manage hormonal treatment and prevent complications [30]. Our cases were stable without complications.
- Non-Secreting Bilateral Adrenal Adenoma: Monitoring is not recommended for benign adenomas < 4 cm, but is indicated for those with indeterminate features, significant size increase (≥20% from initial size), or new clinical symptoms.. In our cohort, no new clinical manifestations were observed in patients
- Bilateral Adrenal Metastases: Follow-up focuses on the primary tumor. Both cases in our series were managed in oncology with regular follow-ups.
- Bilateral Adrenal Lymphoma: Generally poor prognosis [31]. Our patient died during follow-up.
- Bilateral Adrenal Cyst: Cysts usually have a good prognosis but require monitoring for complications [32]. No issues were noted in our series.
- Bilateral Adrenal Hematoma: Generally favorable prognosis, with regular follow-up for adrenal insufficiency [33]. The hematoma resolved with treatment in our series.

V. Study Limitations

- Sample Size: The small sample size limits the study, suggesting the need for future research with larger cohorts.
- Resource Constraints: Some tests , including functional imaging and genetic studies, could not be performed.

Conclusion

Bilateral adrenal masses (BAM) are rare entities, accounting for 10 to 15% of all adrenal masses. In contrast to unilateral masses, the investigation and management of BAM have been less extensively studied in recent decades. Within this context, our study, conducted by the Department of Endocrinology, Diabetology, and Nutrition at Hassan II University Hospital in Fez, focused on 30 cases of BAM, compared with existing literature, with the aim of elucidating their clinical, biological, radiological, therapeutic, and prognostic characteristics.

The clinical presentation of BAM is diverse, ranging from overt symptoms to nearly asymptomatic cases, or incidental findings during cancer staging, secondary hypertension evaluation, or syndromic association screening (such as MEN, VHL, etc.). The biological assessment of BAM involves the same hormonal evaluations as unilateral masses, which helps exclude excessive hormonal secretion by measuring various adrenal hormones and their metabolites. However, when bilateral characteristics are present, it is imperative to exclude the diagnosis of congenital adrenal hyperplasia and adrenal insufficiency.

Imaging techniques are varied and continuously evolving, with abdominal CT scans remaining the gold standard for diagnosis. Therapeutic management depends on several factors: the type of tumor, hormonal profile, tumor size, signs of malignancy, and associated comorbidities. Regular follow-up, with frequency depending on the etiological profile, is crucial to detect any potential recurrences or malignant transformations. Genetic counseling is also essential in familial cases.

Healthcare professionals are encouraged to remain thoroughly informed about the complexities of BAM to ensure precise diagnostic practices and the implementation of optimal management protocols.

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