Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

Endocrinology

Surrenalian Incidentaloma from Diagnosis to Treatment

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Original Research Article

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Article History
Received: 26.02.2018
Accepted: 06.03.2018
Published: 30.03.2018

DOI:
10.21276/sjams.2018.6.3.84

Abstract: The development of medical imaging techniques has increased the accidental diagnosis of numerous silent and ignored tumors. The term "adrenal incidentalomas" refers to an adrenal mass equal to or larger than 1 cm in its main axis discovered by chance during an abdominal imaging examination not motivated by exploration of an adrenal pathology. These incidentalomas can be secreting or not, benign or malignant. These characteristics must be distinguished by the physician to help in choosing the treatment, using biology and imaging, essentially CT without and with injection of a contrast agent. We conducted a two-year prospective study in endocrinology department at Mohamed VI University Hospital of Marrakech, included 19 patients whose average age was 43.42 years with extremes of 31 to 72 years, all admitted for exploration of an adrenal incidentaloma. HBP was found in 6 cases with a rather digestive symptomatology (abdominal pains and / or digestive disorders) initially associating the triad of Menard. The methoxylated urinary derivatives were made in the majority of the cases, making it possible to confirm a pheochromocytoma in 10 patients; dexamethasone test and urinary free cortisol measurement found Adrenal cortical carcinoma (ACC) in 3 cases and shed doubt on subclinical Cushing's syndrome in 2 cases. CT appearance and tumor size suggested malignant ACC in 4 cases. In 16 cases surgery allowed improvement of the clinical symptomatology. Tests must be carefully chosen in order to avoid proposing unnecessary and costly examinations to too many patients and, equally, not to ignore the diagnosis of a malignant or secreting tumor. From these tests, the decision of the type of care management will be made: surgical or monitoring. If simple monitoring, specific criteria and duration must be followed and respected (clinical, imaging and biology).
Keywords: adrenal gland-incidentaloma-diagnosis-treatment.

INTRODUCTION

Adrenal incidentaloma (AI) is an adrenal mass, typically 1 cm long or larger, discovered by chance during an imaging examination motivated by an extra-adrenal call symptom. Its prevalence, established from very large autopsy or imaging series, is about 5% in the general population [1]. It increases with age, from 1% by the age of 30 to 7-10% beyond 70 years [2,3]. The AI are on the right side in 50-60% of cases, on the left side in 30-40% of cases and they are bilateral in 10-15% of patients [4]. The etiologies are diverse [5]. They can be cortical tumors, medullary tumors, malignant tumors of non-adrenal origin, extra-adrenal tumors or lesions of other types. Among these many etiologies, we distinguish the AI secreting or not and AI malignant or not. The secreting AI represents only a minority of AI (15%). The search for a secretion is however systematic, in search of a subclinical hypercortisolism ("pre-Cushing"), a pheochromocytoma, and, only in case of HBP, a primary hyperaldosteronism. The other secretions (virilizing tumor) are exceptionally the origin of an incidentaloma. Malignant Adrenal cortical carcinoma ACC can be secreting basically cortisol and adrenal androgen. In case of non-secreting AI, the threat is to keep growing, in the absence of surgery, to a malignant ACC. A malignant tumor is often mentioned in priority in the presence of an incidentaloma, even if in practice it is a rare event. Among malignant tumors, it is also necessary to exclude metastasis from an extra-adrenal tumor. Bilateral AI represents 15% of all AI. They are suspected of metastasis, congenital hyperplasia, familial pheochromocytoma (NEM2a, von Hippel-Lindau, neurofibromatosis type 1), lymphoma or infectious processes such as tuberculosis. The diagnostic and therapeutic approach must follow that of unilateral AI.

PATIENTS AND METHODS

We conducted a prospective study, starting January 1st, 2014 until December 31st, 2016, in endocrinology department of Mohamed VI University Hospital in Marrakesh including all patients admitted for etiological assessment of adrenal incidentaloma.

RESULTS

We have collected 19 cases. The average age of patients was 43.42 years with extremes from 31 to 72 years. HBP was known in 6 cases and was well managed under treatment in 4 patients. The average oldness of HBP was 14.8 ± 8.67 months. The initial symptomatology was digestive (abdominal pain and / or digestive disorders) which indicated an abdominal CT. A HBP, a triad of Menard was found during history taking in 12 cases. The methoxylated urinary derivatives were made in the majority of the cases, with a high rate in 10 patients confirming a pheochromocytoma; dexamethasone test and urinary free cortisol measurement found Adrenal cortical carcinoma (ACC) in 3 cases and shed doubt on subclinical Cushing's syndrome in 2 cases.

CT appearance and tumor size suggested malignant corticosteroids in 4 cases. Surgery was performed in 16 cases with improvement of clinical symptomatology. The therapeutic abstention was chosen in 3 cases in front of the morphological aspect and locoregional invasion that unfortunately led to the death of 2 patients.

DISCUSSION

Evaluation of adrenal incidentalomas is multidisciplinary, including surgeon, endocrinologist, nuclear physician and radiologist. Clinically, family history and / or personal endocrinopathies must be sought. The clinical examination should include blood pressure and pulse measurement, and focus on highlighting signs, even simple, in favor of abnormal hormonal secretion: obesity, HBP, skin fragility, fatigability and muscle cramps. We can use previous photographs in order to find morphological changes. An adrenal incidentaloma in a patient with a history of treated cancer (mainly lung, kidney, breast, colon or melanoma) is in ¾ of cases a metastasis of his primary cancer [6]. The risk of metastasis to an adrenal incidentaloma is estimated at less than 2% in the absence of any personal cancer history. If there is a history of cancer and isolated adrenal involvement, the risk of metastasis is of 30 to 50% however if the context is that of a multimetastatic cancer, the risk of metastasis is much higher than 50%. On the other hand, if the patient does not have any known extra-adrenal cancer, the AI is exceptionally revealing a primitive and a malignant ACC must be eliminated [6].

With the exception of typical myelolipomas, cysts and hematomas, any AI should lead to a brief biological assessment, even if the patient is asymptomatic and the clinical examination is normal. This makes it possible to distinguish between secretory and non-secretory AI and to specify perioperative precautions (postoperative glucocorticoid substitution in case of Cushing's syndrome, anesthetic preparation, preoperative assessment in case of pheochromocytoma).

The search for a pheochromocytoma is systematic, including normotensive subjects [7]. It can be done by measuring methoxylated derivatives of the catecholamines on the urine of 24 hours with simultaneous measurement of the creatininuria. This test, very widely used, has sensitivity and specificity of 91% and 98% respectively. Plasma free metanephrines test can also be used. Its sensitivity is better (99%), but its specificity is lower [8].

A subclinical Cushing syndrome is often found. It is often benign adenoma and more rarely ACC. Its screening is based on the overnight dexamethasone suppression test [8, 9, 2]. In case of uncertainty, some additional tests may be necessary: measurement of 24-hour cortisoluria, ACTH at 8 o'clock in the morning, salivary cortisol at midnight, or blood DHEA-sulfate (dehydroepiandrosterone sulfate).

The search for an autonomous hypersecretion of aldosterone is only proposed in subjects with HBP and / or hypokalemia (<3.5 mEq / L). Screening for primary aldosterone's is done under neutral antihypertensive therapy (stopping of ACE inhibitors, beta-blockers). It is done by measuring the renin and aldosteronemia in sitting position. Then calculating the ratio of aldosterone on renin, which makes it possible to suspect a primary hyper-aldosterone's

The measurement of androgens (testosterone, DHEA sulfate, 17-hydroxy-progesterone, deoxycortisol) is not systematically recommended, but depends on clinical and radiological data (if suspicion of malignancy) [8].

In case of a bilateral incidentaloma, an infiltrative or tumoral aspect requires the search for adrenal insufficiency with an ordinary synacthene stimulation test. The purpose of the 17-hydroxyprogesterone test is to investigate a 21-hydroxylase enzymatic deficiency and that of ACTH affirms the primary origin of the adrenal deficiency.

If biology is essential to establish the secretory or non-secretory nature of the AI, imaging is a powerful tool for discriminating lesions that are surgical (suspicious and /or secreting: corticosalenaloma, pheochromocytoma ...) and benign lesions that can be monitored. Abdominal CT, with and without injection, is able to define the size and the ratio with the neighboring organs. Thanks to thin sections centered on the adrenal glands, three criteria are analyzed: the size of the lesion, its density without injection, and the study of the late enhancement 10 to 15 minutes after injection which makes it possible to calculate the absolute and relative washout. The risk of malignancy increases with the size of the lesion [4,10]. Above 6 cm, the proportion of malignant tumors is 25%, whereas it is 6% for masses of 4 to 6 cm and less than 2% for masses of less than 4 cm. The different studies carried out make it

possible to identify a threshold of 10 HU below which benignity is almost certain [3]. Post-injection mass enhancement analysis is very useful in low-fat adenomas with a spontaneous density greater than 10 HU, which accounts for 30-50% of adenomas [8]. It allows calculating the parameters of the wash out which reflect the release of the iodinated contrast product by the adrenal lesion which is independently from the lipid contents of the adenomas. A 50% reduction of the wash-out at 10 minutes after injection is typical of an adenoma; minimum values of 40% for the relative wash-out and 60% for the absolute wash-out make it possible to affirm the adenoma with a specificity of 100% [11]. Malignant lesions and, to a lesser extent, pheochromocytomas, generally have a density> 10 HU, are heterogeneous, hyper vascularized and have a reduced wash-out 10 to 15 minutes after injection.

Some AI has typical CT appearance. The hematoma, when seen early, has a high spontaneous density. Myelolipoma is spontaneously hypodense. The cyst is a rounded mass with a thin and regular wall; it has a spontaneous water density and especially it does not enhance after injection of contrast agent.

The MRI does not provide additional diagnostic elements compared to CT. Sensitivity and specificity are 78% and 87% respectively in tissue characterization. Benign lesions have T1 and T2 signal intensity equal to or slightly less than that of the normal liver [12]. Pheochromocytoma present a typical T2 signal; Adrenal gland / liver ratio > 3and a fast and intense enhancement after gadolinium injection. The loss of signal between the in-phase (water and fat) sequences and the anti-phase (water-fat) sequences is an important criterion for characterizing the tumor [13]. A signal decrease in the anti-phase of 20% would be in favor of an adenoma [14]. MRI could therefore be useful in the characterization of AI, especially in the case of impossibility of performing CT with injection of iodinated contrast agent.

Iodine-123- metaiodobenzylguanidine (MIBG) scintigraphy is the usual functional imaging procedure for detecting pheochromocytomas and / or paragangliomas [15,16]. It has a sensitivity of 83-100% and a specificity of 85-100% [21]. It is prescribed when the diagnosis of pheochromocytoma is confirmed in order to eliminate other localization or rare metastases [17], but also before the surgery of an unknown CT mass with methoxyl derivatives borderline or variable at repeated sampling [8]. [18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), by combining PET and CT, has the ability to evaluate the metabolic activity of the adrenal and, at the same time to give morphological information [18, 19]. Often used in case of doubt of metastasis or suspicious lesions that is not typical of adenoma. The tracer uptake by the tumor is calculated visually and through quantitative analysis (SUVmax calculation of the tumor). The ratio SUV max tumor / SUV max liver is calculated: FDG-PET is highly predictive of malignancy for a ratio ≥ 1.45. In front of a hypermetabolic lesion four main diagnoses must be declared: pheochromocytoma, ACC, metastasis, lymphoma [18, 20].

PET 18-F DOPA and PET18F-FDA have the following advantages: fast (2 hours), superior spatial resolution, no drug interference and, in general, no physiological fixation of the tracer in the normal adrenal medulla. Several studies have shown excellent sensitivity equivalent or superior to MIBG scintigraphy in patients with pheochromocytoma and or paraganglioma. PET 18-F DOPA or PET18F-FDA are considered to be superior functional imaging techniques in case of pheochromocytomas associated with Von Hippel-Lindau syndrome and paragangliomas with SDHD mutation [21,22]. I131 (NP-59) iodine-methyl-norcholesterol scintigraphy is poorly performed and is not very specific: it has a sensitivity of 60% for adenomas secreting less than 2 cm in size and 96% for adenomas of size ≥ 2. cm [23]. It may be useful before surgical decision in patients with independent Cushing-ACTH syndrome with bilateral adrenal lesions. In this case, it can show a unilateral fixing, with extinction of the contralateral adrenal. A unilateral adrenalectomy corresponding to the fixing lesion is then proposed. Currently, the French Society of Endocrinology (SFE) proposes to perform this examination as second-line for tumors of 2 to 5 cm of unknown nature to CT, doubtful of subclinical hypercriticism [8].

The biopsy puncture of an adrenal lesion is prohibited, except for patients suspected of adrenal metastasis with known primary cancer. When decided, a pheochromocytoma must be eliminated because the prevalence of pheochromocytoma in a patient with extra-adrenal cancer is relatively high, from 5-9% [24] to 25% [25].

Catheterization of the adrenal veins is an examination that should be discussed only in cases of primary hyperaldosteronism. It is useless in the other indications (hypercorticism) or even dangerous (pheochromocytoma). In a patient with hyperaldosteronism, venous catheterization for aldosterone in the adrenal veins should only be proposed if surgery is considered in a patient over 40, regardless of CT appearance [26]. In a meta-analysis of 38 studies, Kempers et al. have shown that limiting themselves to CT and / or MRI would lead to unnecessary surgery in 18.5% of cases [27].

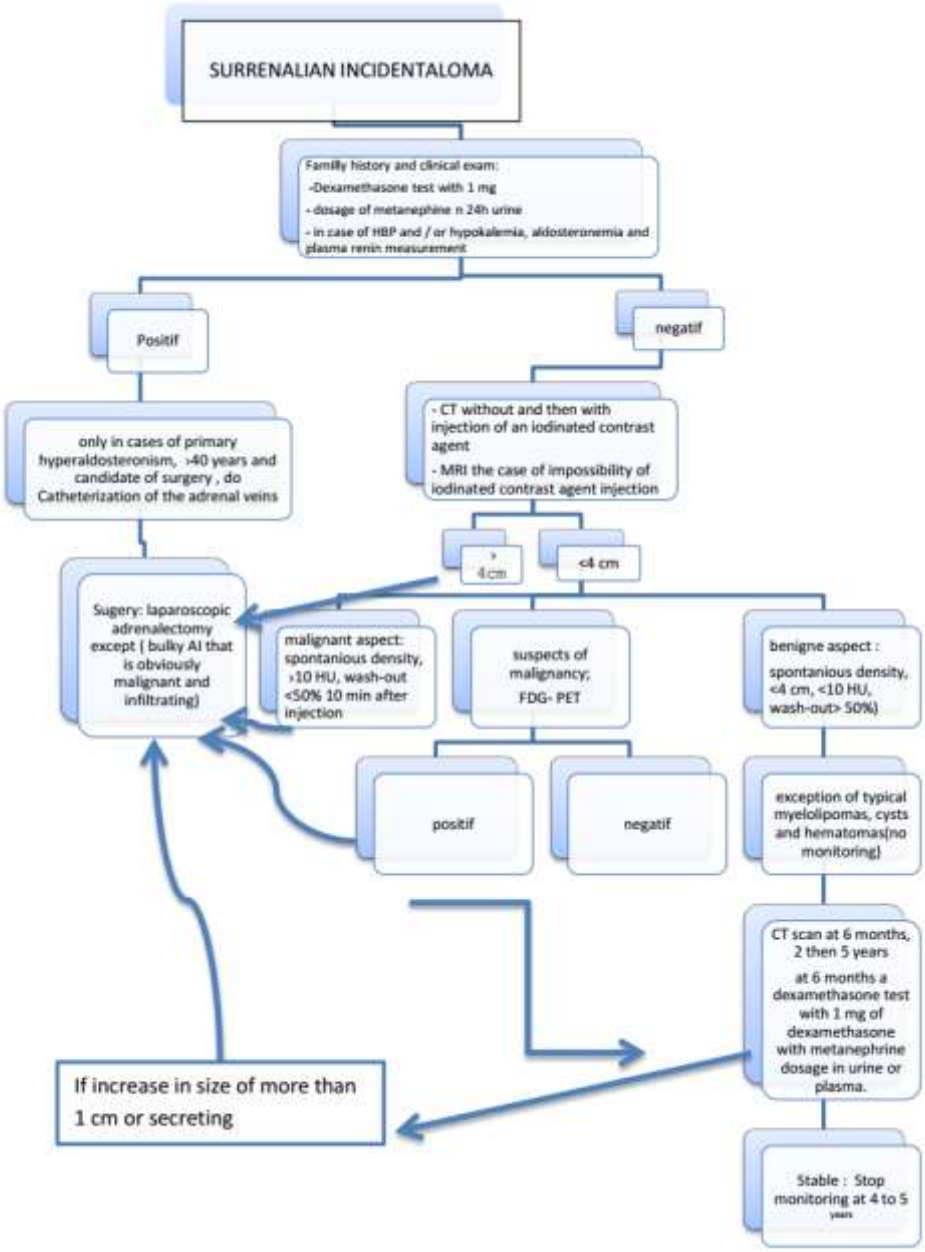

Fig-1: Algorithm for the management of an adrenal incidentaloma

Therapeutic Management

Two main indications are currently recognized: secreting tumors and potentially malignant tumors, to which can be added the particular case of tumors that are locally symptomatic because of their volume and may constitute an indication for surgery, especially when the patient is young [28] (Fig. 1). If no contraindication, any secreting AI (pheochromocytoma, Conn's adenoma, Cushing's syndrome) must be operated, regardless its size [29]. The major problem of secreting tumors is represented by subclinical cortisol adenomas where secretion in the gland is autonomous but insufficient to cause clinical Cushing's syndrome. There are no strict diagnostic criteria, urinary free cortisol is normal in more than half of patients. The dexamethasone test is insufficient. The ACTH rate is low. Noriodocholesterol scintigraphy, if performed, would reveal localized hyperfixation on the incidentaloma side. The risk of progression of these subclinical cortisol adenomas is the evolution toward a Cushing's syndrome but this risk is poorly clarified: if a non-secreting adenoma evolves into a subclinical cortisol adenomas in 6.6% of patients after 5 years of follow-up, subclinical cortisol adenomas would progress to clinical Cushing's syndrome in 12.5% of cases at one year [30].

A prospective controlled study compared 23 patients operated with 22 patients under observation [31]: patients who had adrenalectomy showed an

improvement or a cure of their diabetes in 63% of cases, their HBP in 67%, their dyslipidemia in 38% of cases and their obesity in 50%. On the other hand, many of the non-operated patients experienced a worsening of their diabetes and HBP. Authors concluded that between experienced hands, laparoscopic adrenalectomy was justified for the subclinical cortisol adenomas. These results were confirmed in an Italian study which, in addition, showed that the quality of life of these patients was significantly improved by adrenalectomy [32]. Despite the lack of formal recommendation for the surgical management of subclinical cortisol adenomas, the risk of progression to Cushing's syndrome and the demonstrated improvement of carbohydrate or weight balance disturbed in patients with subclinical cortisol adenomas after adrenalectomy justify surgery in these patients, especially when they are young and when they have carbohydrate abnormalities and extra weight. Otherwise, surgical abstention requires prolonged biological monitoring.

Small-sized myelolipomas, adrenal cysts and hematomas have typical imaging aspects. Given their lack of evolving risk, it is not necessary to complete the biological test for these AI or to monitor them. If AI more than 4 cm in its long axis, adrenalectomy is currently recommended. The increased proportion of malignant ACC beyond this size, their aggressiveness and poor prognosis (survival of 39% at 5 years [33] lead to preferring this surgical attitude.

The main problem faced in front of small - less than 4 cm- AI suspects of malignancy, is that they are not formal indications of FDG-PET. In these cases, in the absence of CT criteria for benignity, FDG-PET is indicated for hyperfixation and a high SUVmax tumor / liver ratio. The removal of these lesions can be performed by laparoscopy, taking away the entire adrenal lining and avoiding any capsular break-in. Metastases, when isolated and the general condition of the patient allows, surgery is then indicated.

Various approaches have been described, including anterior laparotomies (median and / or transverse), lumbotomies, thoraco-phreno-laparotomies, posterior and, since 1992, laparoscopic approaches. This laparoscopic approach was first described by Michel Gagner, of Montreal [34], then very quickly by Yves Chapuis in France [35, 36].The eliminating process consists of an adrenalectomy, enlarged to the adrenal lining for all lesions of undefined diagnosis. In these cases, performing partial adrenalectomy alone removing a small tumor remains formally contraindicated. Laparoscopic adrenalectomy has become the gold standard for the treatment of adrenal lesions (secreting or not) of medium size (<6 cm) but has also been proposed in recent years for large lesions or even potentially malignant but non-infiltrating lesions of small size [37, 38]. Large adrenocortical carcinomas (> 10 cm) and / or invading adjacent structures (stage 3) remain the only indications for immediate laparotomy [39]. The open posterior approach and lumbotomy are no longer practiced for adrenalectomy. Laparoscopic approaches are associated with better results than open surgery in terms of morbidity, preoperative blood loss, postoperative pain and / or analgesic consumption, length of stay, duration of convalescence, and / or the speed at which a professional activity resumes, aesthetic damage, parietal complications, and finally cost [40, 41].

The risks represented while removing a secreting lesion mainly concern pheochromocytomas and cortisol adenomas: a hemodynamics risk as well as metabolic consequences (hypoglycemia) for pheochromocytomas [42], and a risk of corticotropin insufficiency in patients presenting with an incidentaloma responsible for Cushing's syndrome or subclinical cortisol adenomas. This is prevented by a suitable substitution by hydrocortisone.

Monitoring of an unoperated AI

Non-secreting not suspicious AI; The majority of unilateral AI, 70-90%, are small non-secreting adenomas. They can be simply monitored by imaging to diagnose a possible volumetric progress and by biological tests in order to detect any presence of a secretion. Adrenalectomy may be proposed during monitoring. In fact, the lesions considered as benign and non-secreting, presenting a volumetric evolution, become secondarily responsive to an excision. Monitoring of non-operated AI (non-secreting, <4 cm, <10 HU, wash-out> 50%) aims to: "catch up" with possible initial misdiagnosis; to detect a suspicious increase in size or the presence of secretion [8].

Increase in size and risk of cancer; the absence of large cohort studies of sufficient length does not allow to precisely evaluating the risk of degeneration of an adenoma. This risk remains hypothetical. It may be noted, however, that if the initial characterization of the incidentaloma was consistent with the recommendations, the risk of transformation or malignancy is considered to be zero, even with a slow and moderate increase in size [43, 44]. The vast majority of incidentalomas monitored remain stable in volume. If 7 to 10% of AI can increase in size very moderately, in 3 to 5% they decrease [8]. The increase in size of more than 1 cm compared to initial size should burden only if it is fast and in this case the initial diagnosis should be reconsider. A rapidly progressive tumor, doubling in volume or more in less than a year, should be considered very suspicious and should lead to surgery. However, it should be noted that no study has reported a case of ACC diagnosed on the volume increase of an initially monitored AI if all the criteria of benignity, in particular CT, were respected at the time of diagnosis of the AI.

Onset of hormonal secretion; the risk of hormonal secretion to appear during follow-up is also very low. No development of pheochromocytoma or primary hyperaldosteronism is seen during AI monitoring. On the other hand, there is a low risk for cortisol secretion to appear, of the order of 4 to 12% at 3 years [30, 45]. This secretion of cortisol could be linked to subclinical cortisol adenoma, which was not well known during the initial assessment, and which, during follow-up, was revealed as a more frank secretion. The main known risk factor would be an adrenal mass size of more than 3 cm.

There is no agreement on a standardized monitoring scheme, in the absence of high-level evidence, as the duration of follow-up and the numbers of patients included in the published series are often insufficient. The French Society of Endocrinology (SFE) [8] recommends carrying out a CT scan at 6 months to eliminate a volumetric progression which, if it is rapid, is very suspect of malignancy. In the absence of any size changes, SFE proposes a new CT scan at 2 and then at 5 years. For the secretion part, apart from signs of cortisol impregnation such as; (hypertension, weight gain, appearance of a metabolic syndrome), the SFE recommends at 6 months a dexamethasone test with 1 mg of dexamethasone with metanephrine dosage in urine or plasma.

Further than that, SFE recommends to repeat only one dexamethasone test at 2 years and 5 years. NIH, the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons recommend performing imaging at 6 months and then 1 year and 2 years, with annual hormonal control for 4 to 5 years [4, 45, 46]. Beyond this period without volumetric increase or hormonal secretion, monitoring can reasonably be interrupted even if there is no conclusive evidence demonstrating the validity of this attitude.

CONCLUSION

The AI is not uncommon. Their management must take into account their nature (malignancy, secretion), their evolutionary risk (low). It is multidisciplinary and associates surgeons, endocrinologists, radiologists and nuclear physicians. Clinical examination should focus on detecting simple signs of secretion. The biological assessment includes systematic examinations (Dexamethasone test, urinary methoxylated derivatives measurement, and, in case of HBP and / or hypokalemia, aldosteronemia and plasma renin measurement) and others, reserved for special cases. The imaging is dominated by CT without and then with injection of an iodinated contrast agent (size of the lesion, measurement of its density, study of the wash-out). Surgical indications are there for all secretory AI, AI suspected of malignancy (risk of transformation to malignant ACC, some adrenal metastases under specific conditions), and for rare benign large and compressive benign tumors.

The surgical procedure is laparoscopic adrenalectomy, laparotomy being reserved for bulky AI that is obviously malignant and infiltrating. The majority of non-secretory AI can be monitored (<4 cm, <10 HU, wash-out> 50%). Monitoring is clinical, biological and by CT. It can be interrupted after a period of 4 to 5 years in the absence of evolving.

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