Optimizing imaging in adrenal pathology

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Introduction

The rate of adrenal masses identified on computed tomography (CT) or ultrasound scans is 4-6% according to most literature reports. Following identification, it is necessary to establish a differential diagnosis and to perform an accurate characterization of the mass with no need for invasive methods. Currently available imaging techniques enable differentiation of lesions consistent with benignity from those consistent with malignancy, and with the contribution of endocrinologists and laboratory tests, it is possible to differentiate functioning from nonfunctioning lesions.

Some lesions can be immediately characterized if certain features are present: for example, myelolipomas can be identified by low CT density (usually showing macroscopic fat), adrenal hematomas show high density in acute stages and diminished size on follow-up, and cysts can be identified by an association of features inherent to their morphology, no enhancement on intravenous contrast enhanced scans, medical history, type of evolution and growth of the lesion.

Diagnostic difficulties are encountered with the most common lesions: i.e., incidentalomas, nonfunctioning adenomas, metastases and the rarely occurring adrenocortical cancer (ACC). In these processes, the use of an algorithm would provide a guide for proper identification. Differentiation between these lesions has profound consequences for the patient as regards evolution and treatment.
Objective

The aim of this study is to propose an imaging algorithm for adrenal lesions that may allow us to arrive at an accurate diagnosis (from imaging features in combination with clinical symptoms and laboratory findings) and enable characterization of most lesions.

The use of such algorithm might enable an accurate diagnosis in the shortest possible time, reduce patient exposure to radiation, and allow treatment planning and optimization of resources.

Description of the procedure

We retrospectively evaluated 157 patients with adrenal disease from May 2009 to December 2011. The informed consent was signed by all patients; 95 women and 61 men, aged 33 to 78 years old (mean age: 55 years).

The main imaging method was CT. In most cases, a 16-channel Siemens Emotion CT scanner was used, and in a few cases, a spiral CT scanner was employed. The adrenal gland (AG) imaging protocol consisted in obtaining slices without IV contrast, with lesion size and density measurement. If lesion density was greater than 10 Hounsfield units (HU), a dynamic series was performed following the administration of 100 ml of non-ionic iodinated contrast at a flow rate of 3 ml/s. Collimation was 1.5 to 2.5 mm³.

Portal venous (60 seconds) and delayed phase (15 minutes) images were obtained. In addition, lesion density was measured in the portal venous and delayed phases (washout) and the relative percentage washout (RPW) and absolute percentage washout (APW) were calculated according to the following formulas:

- Absolute percentage washout: \( \left( \frac{\text{attenuation at portal venous phase} - \text{attenuation at delayed phase}}{\text{attenuation at portal venous phase} - \text{unenhanced attenuation}} \right) \times 100 \%

- Relative percentage washout: \( \left( \frac{\text{attenuation at portal venous phase} - \text{attenuation at delayed phase}}{\text{attenuation at portal venous phase}} \right) \times 100 \%

Lesion density was obtained with a circular region of interest (ROI), which was not placed in areas with calcifications, bleed-

Figure 1 Diagnostic algorithm proposed by the authors. CECT: contrast-enhanced computed tomography.
ing or necrosis. In a few cases, we encountered difficulties as adrenal lesion features were not consistent with parameters reported in the literature; therefore, in order to make a diagnosis we complemented with magnetic resonance imaging (MRI) or positron emission tomography with the glucose analog 18F-fluorodeoxyglucose (FDG-PET/CT). This is an important tool both for diagnosis and differentiation between benignity and malignancy in adrenal disease, and for pre- and post-treatment staging of adrenal neoplasms.

When indicated by the established algorithm, fine needle aspiration biopsy (FNAB) or surgery was performed (Fig. 1).

Results

In 157 evaluated patients we identified: 59 (49 unilateral and 10 bilateral) nonfunctioning adenomas and 29 functioning adenomas, 9 bilateral hyperplasias, 4 myelolipomas (2 in a patient with simple virilizing congenital adrenal hyperplasia), 2 cysts, 2 hematomas, 3 (2 secondary and 1 primary and bilateral) lymphomas, 30 metastases, 5 adrenal cortical carcinomas, 12 pheochromocytomas, 1 malignant pheochromocytoma, and 1 ganglioneuroma. Fifty-four percent were incidentalomas. All functioning adenomatous lesions, independently of their size, were surgically removed, while adrenal hyperplasias were treated with medical therapy. Non-functioning lesions with a density less than 10 HU were interpreted as adenomas and their growth was evaluated at 6, 12, 18 and 24 months, not requiring contrast-enhanced scans.

In the case of lesions with or without peripheral calcification, with density and morphology consistent with cystic lesions (density < 10 HU and greater than -30 HU on unenhanced CT), an MRI was performed (as these lesions are usually hyperintense on T2-weighted sequences) or the study was completed with CT wash-out. Non-enhancement in the portal venous and delayed phases confirmed the diagnosis.

In nonfunctioning masses with density greater than 10 HU on unenhanced CT and less than 5 cm in size, the washout time was determined. When APW was greater than 60% and RPW was greater than 40%, the masses were considered as lipid-poor adenomas and an unenhanced CT was performed at 6, 12, 18 and 24 months in order to follow-up their growth. In all patients, APW and RPW were analyzed, and no significant or inconsistent differences between both values were observed.

All lesions with density above 10 HU on unenhanced CT with APW below 60% and RPW less than 40% or a size greater than 5 cm were evaluated as probable primary tumors of the adrenal gland or metastasis. The existence of a previous primary tumor in other location led to the use of percutaneous biopsy to confirm metastasis; a prior clinical and laboratory assessment was performed to exclude the possibility of a pheochromocytoma. By this method, a patient was diagnosed bilateral primary B-cell lymphoma.

Pheochromocytomas with positive clinical and laboratory tests were surgically resolved in all cases. In 4 adrenocortical carcinomas, diagnosis was late, as patients had distant metastasis at the time of diagnosis, and no surgery was performed. Just in one patient without metastasis, diagnosis was made by surgery.

In a lesion 6 cm x 3.6 cm, the diagnosis was confirmed by pathology and the lesion was surgically removed (ganglioneuroma). Both in probably secondary lesions and primary masses, FDG-PET/CT was performed when it was required.

The characteristics of the most common adrenal pathology are described below.

Incidentalomas

The term adrenal incidentaloma (AI) is used to define a clinically silent mass discovered unexpectedly in the course of imaging studies (generally ultrasound or CT scans) performed for reasons unrelated to adrenal pathology, in the absence of previous neoplasm or known adrenal disease. According to Aron4, the definition of incidentaloma excludes patients undergoing imaging procedures as a part of staging or workup for cancer. Eighty per cent of AI is benign lesions in patients with unknown history of cancer2,5,6.

With the growing use of imaging, detection of adrenal masses has increased, and these findings are observed in 4-6% of the population studied2,6. Prevalence increases with age, being approximately 8% in autopsy series and 4% on imaging series1,2.

The assessment of AI should be focused on differentiating benign from malignant lesions in order to determine subsequent management, which for example will be surgery in the case of adrenal cancer.

There is a consensus in the literature that any AI requires a thorough clinical, hormonal and radiological assessment to rule out a functioning lesion5. Physical examination and biochemical testing are required to screen for pheochromocytoma, subclinical Cushing and primary aldosteronism, or for less common pathologies, such as estrogen- and androgen-producing tumors.

AI classified as nonfunctioning adenomas will require clinical and imaging follow-up to assess their growth. In these cases, it is necessary to rule out an extraadrenal primary lesion, which would substantially increase the possibilities of secondary lesion1,5.

Twenty-seven percent of oncology patients with extraadrenal
primary lesion have microscopic adrenal metastases, while in 50% of patients with cancer, the presence of adrenal masses will be indicative of metastasis.

**Diagnostic methodology in adrenal incidentaloma**

In all cases of AI, a CT was performed following the AG imaging protocol (i.e. obtaining slices without IV contrast, with lesion size and density measurement). Lesions with a coefficient of attenuation equal or below 10 HU and above -30 HU in slices without iodinated contrast were considered to be adenomas and were followed up at 6, 12, 18 and 24 months to assess their growth. No further studies were required (fig. 2). When the lesion density was above 10 HU, a dynamic series was performed following the administration of 100 ml of iodinated contrast. Density of the lesion was measured in the portal (60 sec.) and delayed (15 min.) phases, and APW and RPW were calculated.

Lesions with density between 10 and 20 HU were classified as indeterminate and were further evaluated with contrast, measuring washout time, APW and RPW (with the established formulas). In all cases, both percentages were calculated.

The lesion was consistent with adenoma when the APW was greater than 60% and the RPW was greater than 40% at 15 minutes. Lesions with an APW of less than 60% and a RPW of less than 40% were considered as non-adenomatous lesions (fig. 3).

Lesions with density less than -30 HU were diagnosed as myelolipomas and when further workup was necessary, an ultrasound or MRI was performed.

An analysis of published reported results indicates that the value of 10 HU represents an optimal combination of high specificity (96-98%) and moderate to high sensitivity (71-73%) in the diagnosis of adenoma.

In order to determine the size of the lesion, the major diameter was measured in axial slices. Patients with nonfunctioning masses less than 4 cm considered as non-adenomatous on unenhanced CT and with no concomitant neoplastic lesion were followed up by unenhanced CT at 6, 12, 18 and 24 months to assess lesion growth. If no enlargement was observed, lesions were considered to be benign, in agreement with other authors.

![Figure 2](image1.jpg) Fifty-six year-old female patient with left adrenal incidentaloma. Density of the lesion on unenhanced CT was -3 HU, and it was diagnosed as a lesion consistent with nonfunctioning adenoma. Diagnosis was confirmed at 24-month follow-up.

![Figure 3](image2.jpg) (a) Fifty-five year-old female patient. Incidental finding of a right adrenal lesion of 31 HU, acquired without IV contrast. Because of suspected metastasis or malignancy, washout was ordered. (b) In portal phase, density of the lesion was 71 HU. (c) In the delayed phase (at 15 minutes), density was 44 HU, with washout below 50%. This confirmed the diagnostic impression. A subsequently ordered CT scan of the chest showed a primary pulmonary lesion, confirmed as lung adenocarcinoma by FNAB. A staging FDG-PET/CT scan showed a hypermetabolic lesion in the right adrenal gland.
Adenomas

Adenoma is the most common adrenal lesion. It is detected in 0.14 to 2% of abdominal CT in patients aged 20 to 29 years, and in 7 to 10% of CT in patients older than 70 years old13,14. Of these lesions, 94% are nonfunctioning.15

There are no specific morphological features that may lead to diagnosis of adenomas when discovered, but they are typically small, with well-defined borders and homogeneous in attenuation on precontrast images and in 58% of postcontrast images.

Although size is not a definitive indicator of benignity, most publications include adenomas within the range of 2-2.5 cm. Other authors report adenomas of up to 6 cm16,17.

Adenomas are slow-growing lesions but in rare cases they may experience a sudden increase in size by stimulation of elevated levels of adrenocorticotropic hormone (ACTH) or as a result of hemorrhage. In patients with adenomas and concomitant anticoagulation therapy, hemorrhage has been found to result in heterogeneity and enlargement of the adenoma, consistent with pathological findings16.

Seventy percent of adrenal adenomas contain intracellular fat (cholesterol, fatty acids and neutral fat) in contrast with malignant lesions, and therefore adenomas have lower density than primary tumors and metastases on unenhanced CT.8,13 Lee et al.8 were the first to differentiate images consistent with adenomas from non-adenomatous lesions on unenhanced CT. While in adenomas mean attenuation was -2.2 HU, in non-adenomatous lesions attenuation reached 28.9 HU18.

A meta-analysis published a posteriori showed that at a threshold of 10 HU, sensitivity increased to 71% and specificity remained at 98%13.

If the attenuation of the lesion is over 10 HU on unenhanced CT (indeterminate), contrast-enhanced CT should be performed and washout calculated1,3,5,8. Caoili et al.3 demonstrated that, independently of their fat content, adenomas had a fast washout, an APW above 60% and a RPW above 40%, unlike tumors and metastases6,10,18,19. Usefulness of magnetic resonance imaging and 18F-fluorodesoxyglucose positron emission tomography in differential diagnosis.

Adenomas with intracytoplasmatic fat show signal loss at chemical shift MR imaging on out-of-phase images, as compared to in-phase acquisition. A signal loss greater than 20% is considered diagnostic of adenoma (fig. 4)15,20,21.

Adenomas poor in intracytoplasmatic fat account for 10 to 40%. This implies that a large number of incidentalomas cannot be distinguished from metastases, primary tumors or other lesions deficient in intracellular fat, with the MRI out-of-phase chemical shift technique15.

When the lesion shows non adenomatous characteristics on CT and MRI, subsequent management depends on the size of the lesion. In our study, surgery was considered for lesions greater than 4 or 5 cm.

The use of FDG-PET/TC enables the detection of increased metabolic activity in an adrenal lesion, which often appears indeterminate on CT and MRI1,2,15.

In hybrid scanners, CT provides improved spatial and contrast resolution, allowing better anatomical location of the tumor and density measurement. Thus, the use of FDG-PET/CT combines the diagnostic possibilities of both methods3,7,15.

If the clinical assessment does not exclude the possibility of pheochromocytoma and laboratory findings are inconclusive, the lesion may be further studied by scintigraphy and FDG-PET/CT, as these tumors are highly hypermetabolic15,22.

Adenomas have minimum metabolic activity, similar to the liver. When avidity for FDG is increased compared to the liver, and the lesion is indeterminate on CT, or the patient has a known primary tumor, the diagnosis of adenoma is ruled out. Moderate false positives have been reported and some investigators suggest that this depends on the functional status of adenomas or on their low fat content.

Other indications for FDG-PET/CT are non-adenomatous lesions on CT and MRI that are associated with clinical and laboratory findings indicative of lymphoproliferative disease. This test may be of diagnostic value for secondary lymphoma and it is used for post-treatment follow-up of this lesion.

The presence of a primary lesion in any other organ and of

Figure 4 Sixty-year-old male patient with a lesion in the left adrenal gland, hypo intense as compared to the spleen on MRI out-of-phase chemical shift image, consistent with lipid-rich adenoma.
non-adenomatous lesion in the adrenal gland(s) is also an indication for FDG-PET/CT to confirm or rule out metastasis and for primary lesion staging\textsuperscript{18,23,24}. Collision tumors (coexisting myelolipoma and metastasis or metastasis and adenoma) are difficult to diagnose only by CT. In patients with a history of malignancy, FDG-PET/CT is helpful for identifying adrenal metastatic lesions, which are markedly avid for FDG\textsuperscript{12,24}.

**Benign lesions associated with adrenal insufficiency or hyperfunction**

**Cushing’s syndrome**

Cushing’s syndrome of adrenal origin is caused in most cases by adenomas 2 to 4 cm in size. A lesion larger than 4 cm with central necrosis is suggestive of adenocarcinoma. In Cushing disease, the most common cause of endogenous Cushing’s syndrome is a high ACTH level from the pituitary gland. As there is bilateral adrenal hyperplasia, both glands are diffusely and uniformly enlarged (fig. 5). Occasionally, bilateral macronodular enlargement is observed. In chronic diseases, the gland may become nodular in appearance, which is known as multinodular hyperplasia. Although these lesions are ACTH-dependent, they may sometimes become ACTH-independent, in which case the entity is known as massive macronodular hyperplasia.

In addition, ACTH-dependent Cushing’s syndrome is caused by ectopic ACTH-secreting tumors, usually from the lung or mediastinum, including, but not limited to, oat cell carcinoma and bronchial or thymic carcinoid. Chest CT scans are very useful for localizing these lesions, in combination with previous confirmation of relevant simultaneous secretion products\textsuperscript{22,25,26}.

![Figure 5 Bilateral adrenal hyperplasia in Cushing's syndrome.](image)

**Conn’s Syndrome**

Conn’s Syndrome (or primary aldosteronism) results from excessive aldosterone production. It is classically caused by adenomas in 80% of cases and by bilateral adrenal hyperplasia in 20%. However, the frequency of adrenal hyperplasia has increased in recent years, mainly if we consider that although the entity was originally described as presenting with hypertension and hyperkalemia, normokalemia may also occur\textsuperscript{27}. Adenomas may be visible on CT in 70% of cases. In recent reviews, aldosteronomas detected by CT had a mean diameter of less than 2 cm; therefore, when this syndrome is suspected, tomography should be performed with reconstructions less than 5 mm thick.

On unenhanced CT, adenoma appears as a hypodense nodular lesion, while in the contrast series, there is no difference from nonfunctioning adenoma\textsuperscript{23}.

Adrenal gland hyperplasia may have normal, nodular and sometimes multinodular appearance. One or both glands may be enlarged and, in those cases, medical treatment is indicated. When CT scan shows normal adrenal glands, bilateral or unilateral nodules, with evidence of associated hyperplasia, these findings should be correlated with functional laboratory tests for disease characterization\textsuperscript{23,27}.

**Adrenal virilization and feminization**

Benign or malignant adrenal cortical tumors sometimes cause virilization and, more rarely, feminization. Benign tumors are 2 to 6 cm in diameter, with a homogeneous appearance, while carcinomas tend to be larger and heterogeneous\textsuperscript{26}.

Addison disease or primary adrenal insufficiency

Addison disease is a primary adrenal insufficiency that may develop as an acute or chronic condition. Acute disease is rare and it may result from bilateral adrenal hemorrhage (apoplexy), generally due to severe shock and sepsis, and sometimes associated with bleeding diatheses\textsuperscript{28,29}.

Bilateral hematomas caused by trauma occasionally result in adrenal insufficiency, which manifests a few weeks after trauma. Identification of bilateral adrenal hematomas on CT scans may be the first indication for diagnosis, as clinical manifestations are nonspecific. In this respect, the role of CT is critical because it shows enlargement of both adrenal glands, with central necrosis and ring-shaped contrast enhancement.

For bilateral adrenal masses, when other pathologies are ruled out by complementary workup, CT-guided aspiration biopsy may be performed to determine the etiology, which might be adrenalitis secondary to tuberculosis (TBC), histoplasmosis, other fungal infection or primary bilateral adrenal...
lymphoma. From this perspective, it is important to highlight that, prior to biopsy, the possibility of pheochromocytoma should be ruled out.

Even if CT provides little information in the case of patients with chronic Addison disease, compared to acute forms, in certain cases it may suggest the cause of disease. Idiopathic atrophy of the adrenal glands probably due to autoimmune abnormality is the most frequent cause of Addison disease, followed by tuberculous granulomatous infection and histoplasmosis, according to the international literature. However, locally, TBC is the prevalent cause.

CT findings in idiopathic Addison disease include involvement of both glands, which appear small, atrophic and with no calcifications. Calcifications occur in 50% of patients with Addison disease secondary to TBC. Nevertheless, bilateral adrenal calcifications are not specific to previous granulomatous infection and cannot be distinguished from idiopathic calcifications or from those resulting from previous adrenal hemorrhage (fig. 6). Clinical and hormonal correlation is essential, as there may be adrenal glands with irregular calcifications and normal function. The mere presence of calcifications does not imply adrenal function involvement.

Non-adenomatous benign adrenal tumors

Myelolipoma

Myelolipoma is a benign tumor composed of hematopoietic and mature adipose tissues. This tumor can arise as an asymptomatic mass in the adrenal gland or from an extraadrenal location, and it is generally diagnosed incidentally. If there are symptoms, they are generally due to mass effect (because of the large size of the tumor) or to intratumoral hemorrhage. When myelolipomas bleed, they may cause pain, nausea, vomiting or hypotension. Myelolipomas are mostly nonfunctioning and unilateral tumors (68 to 78%), of variable size (between 2 and 15 cm), with well-defined borders, high fat content (50 to 90%) and soft tissue density areas.

The typical feature on CT is a variable attenuation between -30 and -115 HU (a much lower density than that of adenomas). Calcifications may occur in some cases (20%), probably related to previous hemorrhage. Contrast-enhanced CT may show an enhancement of the soft tissue component, which may mask fat attenuation.

In the presence of bleeding, CT may detect high- or low-attenuation collections, depending on the stage of hemorrhage. Myelolipomas also have typical MRI imaging features. Because of their fat component, they appear hyperintense on T1-weighted sequences. The use of fat suppression techniques helps to confirm diagnosis, showing a loss of signal intensity in fatty areas.

Myelolipomas may be classified into three groups based on their MRI imaging characteristics: a) homogeneous and hyper intense tumors on T1-weighted images with intermediate signal intensity on T2-weighted images (a finding suggestive of predominantly fatty lesions); b) heterogeneous with areas where signal intensity is equal to that of fat, mixed with areas of high signal intensity on T2-weighted images, or with post-gadolinium enhancement on T1-weighted images (this indicates a mixed adipose lesion with areas of myeloid tissue); c) nodules which appear hypointense on T1-weighted images and hyperintense on T2-weighted images relative to the liver, and which enhance on post-gadolinium images (indicative of lesions predominantly composed of myeloid tissue). The appearance of myelolipomas on ultrasound varies depending on individual tumor proportions of hematopoietic and fat tissue. They frequently have hypo- and hyper-echogetic areas, reflecting the variable amount of fat and myeloid tissue. In predominantly fatty tumors, a uniform hyperechogetic mass is observed, while in tumors with predominantly myeloid tissue, the mass appears hypo echogenic. Myelolipomas that exist in conjunction with other pathologic conditions are significantly different from isolated myelolipomas, they are smaller (mean, 7cm) with less fat (generally <10%), a higher prevalence of calcification (52%) and lower frequency of pseudocapsule (33%).

We should bear in mind that a number of adrenal tumors of different etiology may demonstrate focal macroscopic fat.

Figure 6 Bilateral adrenal calcifications in an asymptomatic patient.

These include adenomas, pheochromocytomas, adrenal cortical carcinomas and metastases. Collision tumors are formed by coexisting lesions of different pathologic origins and manifest with atypical imaging appearances. A collision tumor resulting from the association of a functioning adenoma and a myelolipoma may manifest with hormonal syndrome owing to the adenomatous component. In our series, we found a simple virilizing congenital adrenal hyperplasia with bilateral myelolipomas. Because of the concomitant hormonal syndrome, the patient underwent surgery and the diagnosis of simple virilizing congenital adrenal hyperplasia with bilateral myelolipomas was made by pathology. Myelolipomas are not FDG-avid on PET/CT; however, there are rare cases of FDG-avid myelolipomas because their hematopoietic component may be hypermetabolic.

**Hemangioma**

Adrenal hemangiomas are rare benign tumors (less than 30 cases are reported in the literature) and are typically found incidentally. On unenhanced CT, hemangiomas are well-defined masses, which appear hypodense or with heterogenous attenuation. In one third of cases they may contain irregular calcification from prior hemorrhage, thrombosis or necrosis. Intratumoral phleboliths are characteristic of hemangioma. Contrast-enhanced CT shows multiple markedly enhanced peripheral nodular areas and persistent pools of peripheral enhancement on delayed imaging. Centripetal enhancement as reported in cavernous hemangiomas of the liver is rare, because of the presence of central thrombosis, necrosis and fibrosis.

**Ganglioneuroma**

Ganglioneuromas are benign neurogenic tumors derived from sympathetic ganglia. These tumors can arise from anywhere along the paravertebral sympathetic plexus and may occasionally arise in the adrenal medulla. They are composed of mature Schwann cells, ganglion cells and nerve fibers. The most common locations are the retroperitoneum (32-52%), the posterior mediastinum (39-43%) and the neck (34-36% (8-9%)). In a series of 46 patients with abdominal ganglioneuromas, the tumor was located in the extraadrenal retroperitoneum in 59% of cases and in the adrenal gland in 41%. Ganglioneuromas, unless extremely large, are asymptomatic. The most common clinical manifestations include abdominal pain or palpable mass. Hormonally active tumors secrete catecholamines, vasoactive intestinal peptides or androgens, resulting in symptoms such as hypertension, diarrhea or virilization.

On CT or MRI, adrenal or retroperitoneal ganglioneuromas appear as well-circumscribed oval or lobutaled masses, which tend to encase blood vessels either totally or partially. On unenhanced CT, these tumors are homogeneous with less attenuation than muscle. Discrete and punctuate calcification may occur in up to 20% of cases. On contrast-enhanced CT, these tumors show varying degrees of enhancement, from slight to intense. On MRI, ganglioneuromas are homogeneous with low to intermediate signal intensity on T1-weighted images. The signal intensity of T2-weighted images depends on the proportion of mixoid stroma, cells and collagen fibers. A tumor rich in cellular components and collagen fibers with only a small percentage of mixoid stroma will have an intermediate to high signal intensity on T1-weighted images, while a tumor with a large proportion of mixoid stroma and low amounts of cells and fibers will be hyperintense on T2-weighted images. Nuclear imaging studies, such as metaiodobenzylguanidine (MIBG) or 123-iodine scintigraphy, can identify areas of increased radiotracer uptake, reflecting catecholamine-producing sites. The usefulness of PET/CT in ganglioneuromas is not well es-

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**Figure 7** Patient with normal blood pressure and long-standing discomfort on the left lumbar region. Normal laboratory tests, with no relevant family history. Non-adenomatous lesion in the left adrenal gland, 6 cm in diameter, with a density of 22 HU on unenhanced CT (not shown). On contrast-enhanced CT, density did not largely increase (27 HU). Surgery was indicated based on lesion size and non-adenomatous characteristics. Pathology: ganglioneuroma.
tablished and biopsy or surgery is very often required to confirm benignity. In our series, we found one case of ganglioneuroma, initially diagnosed as incidentaloma. Because of the tumor size and density, surgical management was indicated.

Cysts

Adrenal cysts are incidental findings on CT. They are usually unilateral and solitary lesions, with a 3:1 female prevalence, mostly diagnosed between the ages of 50 and 60 years. Adrenal cysts are asymptomatic, unless they produce a mass effect upon adjacent structures or are complicated with hemorrhage or infection. Cysts are classified into parasitic and non-parasitic.

Non-parasitic cystic lesions are divided into three categories based on histological findings: endothelial cysts (48%), pseudocysts (42%) and epithelial cysts (10%). Endothelial cysts may be angiomatous or lymphangiomatous. Adrenal cysts most commonly occur as multiple, small (1 to 15 mm) lesions, which may be loculated; they rarely occur as large and solitary lesions. Large lymphangiomatous cysts are known as cystic lymphangioma. On unenhanced CT, these lesions are hypodense, while on MRI they appear as thin-walled lesions, hypointense on T1-weighted images and hyperintense on T2-weighted images. Pseudocysts are the most common type of adrenal cysts. They may show septa, hemorrhage or calcification and mostly result from prior hemorrhage in a normal gland or in an adrenal tumor with subsequent clot organization.

Epithelial cysts include unusual cystic adenomas and retention cysts or embryonic remnants. On CT, they show the typical characteristics of any cystic lesion: hypodense with thin walls (less than 3 mm) and internal septa. In addition, they are usually round or oval and occasionally lobulated; curvilinear or peripheral calcification may occur in 15% of cases. Cysts without calcifications may be indistinguishable from adenomas because of their similar attenuation on CT. Contrast-enhanced CT with washout calculation demonstrates the true nature of adrenal cysts, as they do not enhance with intravenous contrast. In less than 20% of cases, benign cysts may show hyperattenuation on unenhanced CT (> 60 HU because of cystic hemorrhage). The only differential diagnosis that might be considered is cystic adrenal adenoma. However, as they have solid areas, these tumors are never only cystic in nature.

Pheochromocytoma

Pheochromocytomas are rare catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla. In most cases, it occurs as an occasional disease, but it has been reported that in 10 to 24% of cases it may develop as a family condition associated with multiple endocrine neoplasms (MEN), neurofibromatosis, von-Hippel-Lindau disease, Sturge-Weber syndrome and tuberous sclerosis.

This tumor usually manifests clinically and it is unilateral; 10% may be bilateral, malignant or extraadrenal, located along the sympathetic nervous system ganglionic chain. The diagnosis of pheochromocytoma depends on detection of adrenal mass in the appropriate clinical setting. The most frequent manifestation is hypertension associated with adrenergic symptoms, confirmed by typical laboratory abnormalities. Twenty percent of these tumors are not detected by biochemical assessment and only 10% are discovered incidentally (although some authors report up to 25%). At CT, most lesions are smooth and round, with attenuation similar to that of soft tissue and malignant lesions, and significantly higher than that of adrenal adenomas. Mean attenuation is 39 ± 14 HU for adrenal carcinomas, 44 ± 11 HU for pheochromocytomas and 8 ± 18 HU for adenomas.

Large lesions are often heterogenous, necrotic or cystic, and are usually non functioning. They are known as “the great pretender” because of their highly varied presentation on imaging.
Attenuation values of malignant lesions and pheochromocytomas increase following the administration of intravenous contrast medium. Washout characteristics are similar to those of malignant lesions and adrenal metastases, regardless of whether the pheochromocytoma is malignant or benign. Traditionally, it had been thought that the use of intravenous contrast medium at CT could precipitate a hypertensive crisis, but the use of nonionic contrast medium has significantly reduced this risk (both in our case series and in literature reports).

In our experience, and in agreement with other authors, we have not seen side effects, such as hypertensive crisis. There are no differences in imaging parameters between incidental and symptomatic pheochromocytomas, but none of them has attenuation values below 10 HU on unenhanced CT.

On T1-weighted MRI images, pheochromocytomas are isointense to liver, kidney and muscle, and 70% of lesions demonstrate high signal intensity on T2-weighted images. This finding can help in the diagnosis of extraadrenal disease. This high signal intensity on T2-weighted images was classically known as “the light bulb sign”, and was originally thought to be characteristic of pheochromocytoma. Currently, however, this idea is no longer considered to be valid because at least 30% of pheochromocytomas show moderate or low T2-weighted signal intensity, appearing similar to other adrenal diseases.

Pheochromocytomas do not usually have significant lipid content and generally maintain their signal intensity in the fat-suppression phase. However, there may be exceptions because fatty degeneration is sometimes known to occur. Most lesions show intense enhancement after intravenous (IV) contrast injection.

At MRI spectroscopy, pheochromocytomas were found to have a choline peak at 6.8 ppm that is not seen in adenomas and is attributed to the presence of catecholamines and catecholamine metabolites. Even if MRI and CT have about 95% sensitivity and 70% specificity for detection of adrenal pheochromocytomas, MRI has higher sensitivity (90%) than CT for detection of extraadrenal lesions. These lesions occur in the abdomen (97%), chest (2-3%) and neck (1%).

In these cases, scintigraphy can be very helpful in diagnosis, as Iodine-123-MIBG or iodine-131 is concentrated within pheochromocytomas. Its use is also helpful in patients with strong biochemical evidence of tumor but no CT evidence of disease and for confirmation of extraadrenal or metastatic disease. Scintigraphy has almost 100% specificity and 95-100% sensitivity for the diagnosis of pheochromocytoma. However, with the increasing availability of PET, scintigraphy is less often performed.

Shulkin studies have shown in the detection of benign pheochromocytomas that MIBG scintigraphy has 83% sensitivity and FDG-PET has 58% sensitivity, while for malignant pheochromocytomas, scintigraphy has 88% sensitivity and PET has 82% sensitivity. Despite the improved sensitivity shown by MIBG, all MIBG-negative lesions proved to be FDG-avid. Thus, in the above-referenced study, authors concluded that most pheochromocytomas accumulate FDG, although the uptake percentage is higher in malignant tumors compared to benign lesions. The authors further concluded that PET performed after administration of FDG is particularly useful for localization of pheochromocytomas that do not accumulate MIBG.

PET imaging with fluorodopamine and carbon 11-hydroxyephedrine has also shown promising initial results for detection and characterization of pheochromocytoma, as these tracers show uptake both in benign and malignant tumors (even if tracer uptake is more significantly increased in the latter).

For extraadrenal tumors, specific tracers for the sympathetic system, 11C- hydroxyephedrine (SUH) and 18-dihydroxy-phenylalanine (18F-DOPA), are being investigated and have shown promising results.

Hematomas

Adrenal hematomas may be spontaneous or traumatic (occurring after severe trauma). Adrenal hematomas resulting...
from blunt trauma arise from the adrenal medulla and extend to the cortex, appearing as round or oval lesions. Lesions occur on the right side in 90% of cases due to compression of the adrenal gland between the spine and the liver, rupture of perforating venules of the adrenal capsule occurs due to deceleration forces and a rapid rise in adrenal venous pressure as a result of inferior vena cava compression. Unenhanced CT is the method of choice for detecting adrenal injury, especially hematoma. The most common imaging feature of adrenal injury is a round to oval hematoma (83%), followed by diffuse irregular hemorrhage obliterating the gland (9%) and uniform adrenal enlargement (9%). Peri-adrenal hemorrhage is usually present and is evidenced by an ill-defined adrenal margin, periadrenal stranding, and asymmetric thickening of the diaphragmatic crus. Hematomas vary in attenuation depending on their age. Acute to subacute adrenal hematomas have increased attenuation on unenhanced scans ranging from 50 to 90 HU. They gradually diminish in size and attenuation at follow-up CT, showing a characteristic hypodense peripheral halo. Calcifications may develop a few months after hemorrhage. MRI is the most sensitive and specific method for diagnosing adrenal hemorrhage. MRI imaging appearance depends on the stage of hematoma. Spontaneous hematomas are associated with anticoagulant therapy or with stress caused by surgery, pregnancy, sepsis, burns or hypotension. Non-traumatic hematomas can be either unilateral or bilateral. They are round or oval and may contain periadrenal hemorrhage. The attenuation of these lesions depends on the age of the hematoma.

Granulomatous infections

Tuberculosis is the most common infectious cause of Addison disease (10-30%). CT imaging findings depend on the stage of disease and degree of activity of the inflammatory process. In the early stages of the infection CT demonstrates “adrenalitis”, consisting of bilateral adrenal enlargement with central necrosis. Contrast-enhanced CT shows hypodense glands with peripheral rim enhancement. Adrenal atrophy and calcification develop at the healing stage. In this stage, the appearance of the gland at CT is similar to that of other chronic granulomatous infections, previous hemorrhage or idiopathic calcifications. Disseminated histoplasmosis usually occurs in endemic areas and in immunocompromised patients with human deficiency virus (HIV) or with neoplasms, lymphomas, etc. About 50% of patients with disseminated histoplasmosis develop Addison’s disease (if untreated, adrenal insufficiency due to histoplasmosis is fatal). CT shows bilateral and symmetrical enlargement of adrenal glands with central hypodensity and peripheral enhancement after contrast. Adrenal glands involved may exhibit different degrees of calcification depending on the stage of infection. Diagnosis may be performed by CT-guided fine needle aspiration biopsy and the pathologist should be made aware of the suspected diagnosis of fungal infection so that the appropriate histological techniques (Giemsa, PAS, Gomori-Grocott or hematoxylin-eosin), cultures (Sabourad or mycobiotic agar) or immunological methods can be used.

Figure 10 (a) Forty-two year-old patient with dyspnea, irritability, weight gain and hypertension of 6 months duration. Physical examination: central obesity, red wine-Colored stretch marks of 2 months duration in the abdomen. Blood pressure: 170/110. Solid lesion in the left adrenal gland. On unenhanced CT, lesion density is 42 HU, the size of the lesion measured on CT is 6.4 cm x 6.9 cm (asterisk). (b) Same patient: T1-weighted contrast-enhanced MRI image shows lesion enhancement (asterisk). (c) Same patient: AT chemical shift MRI, on out-of-phase imaging, the lesion appears hyperintense to the spleen, evidencing an absence of fat content (asterisk). Pathology diagnosis: adrenal cortical carcinoma. Patient survival: 8 months.
Malignant adrenal tumors

Adrenal carcinoma

Adrenal cortical carcinoma (ACC) has a peak incidence in the first and fourth decades of life, and it is more common in women (3:1). ACC accounts for 0.02-0.2% of all cancer deaths and tends to be functioning (50%). This tumor secretes more than one steroid hormone (glucocorticoid + mineralocorticoid or glucocorticoid + androgens), manifesting as Cushing's syndrome, feminization, virilization or mixed Cushing's syndrome – virilization.

Patients may present with hypertensive episodes or local symptoms such as pain, palpable mass or gastrointestinal complaints.

ACC are typically large masses (larger than 6 cm). This feature, associated with rapid growth and metastasis is a criterion for malignancy.

The incidence of metastasis increases by 71% if the lesion is larger than 4 cm or growths within one year of diagnosis. ACC should be suspected when a rapidly growing lesion is found in a patient without a known history of primary malignant tumor in other location, as it is unlikely that a malignant lesion may remain stable for over 6 months.

On unenhanced CT, this type of carcinoma may be heterogeneous (owing to the presence of necrosis) and density is usually above 30 HU. After IV contrast injection, carcinoma enhances heterogeneously, often peripherally, with a thin rim of enhancing capsule seen in some cases.

At CT with washout calculation, ACC has a RPW of less than 40%. However, the large size and the rapid growth of the lesion are the most reliable indicators of the diagnosis (fig. 10a and 10b).

In 19-33% of cases, calcifications have been identified, more commonly microcalcifications. At chemical shift MRI, on out-of-phase images, ACCs, as all malignant lesions, typically appear hyperintense relative to the spleen because of the absence of intracytoplasmatic fat (fig. 10c).

The liver is the most common metastatic location, but other sites include the lung and lymph nodes, along with direct extension and tumor thrombus. Invasion of the inferior vena cava is a well-known complication of this tumor, and it may cause abdominal pain, lower extremity edema or pulmonary embolism.

Cytology is of little value, therefore FNAB is not indicated. When masses arising in the region of the adrenal gland become large, it can be difficult to determine their origin.

FDG-PET/CT is a very effective method for classification and staging of ACC because of the high avidity of this tumor for FDG; it is also effective for detecting metastasis of ACC in 30% of patients. The use of this method modifies the management protocol in 20% of patients.

The only feasible treatment is surgical management when the lesion is small and no metastasis is detected. The prognosis is very poor with a 5-year survival rate of 0%.

Figure 11  (a) Hypertensive patient with high levels of catecholamine. Left adrenal lesion 5.3 cm in diameter, with density of 37 HU on unenhanced CT (not shown) and poor enhancement on contrast-enhanced CT (asterisk). The internal border of the lesion is irregular. (b) Same patient. Lateral aortic retroperitoneal lymph node enlargement interpreted as metastasis (arrow). Pathology diagnosis: malignant pheochromocytoma with metastasis in regional lymph nodes.
Malignant pheochromocytoma

Malignant pheochromocytoma is most common in family MEN II syndromes and multiple tumors. This tumor is characterized by invasion of the adrenal capsule, vascular pedicle and metastasis to adjacent retroperitoneal lymph nodes, liver and bone (fig. 11).

PET/TC imaging with FDG, fluorodopamine and carbon 11-hydroxyephedrine has also shown promising initial results for detection and characterization of pheo-chromocytoma, as these tracers show uptake both in benign and malignant tumors (even if tracer uptake is more significantly increased in

the latter) 7 nevertheless, the only finding that confirms the diagnosis of malignant pheochromocytoma is the presence of metastasis.

Shulkin studies have shown for detection of benign pheochromocytomas that MIBG scintigraphy has 83% sensitivity and FDG-PET has 58% sensitivity, while for malignant pheochromocytomas, scintigraphy has 88% sensitivity and PET has 82% sensitivity.

Certain drugs, such as labetalol, calcium blockers, some antidepressants or sedatives, among others, may inhibit MIBG uptake and should therefore be discontinued at least one week before the study.

Despite the improved sensitivity shown by MIBG, all MIBG-negative lesions proved to be FDG-avid. Therefore, Shulkin concluded that most pheochromocytomas accumulate FDG, although the uptake percentage is higher in malignant tumors compared to benign lesions, and that PET performed after administration of FDG is useful for localization of pheochromocytomas that do not accumulate MIBG45.

For extra adrenal tumors, specific tracers for the sympathetic system, 11C- hydroxyl-ephedrine (SUH) and 18-dihydroxy-phenylalanine (18F-DOPA), are being investigated and have shown promising results45.

Lymphoma

Extra lymphatic involvement is more frequent in non-Hodgkin lymphoma than in Hodgkin lymphoma. The adrenal gland may be a primary or secondary location of non-Hodgkin lymphoma. Primary adrenal lymphoma is much less frequent

Figure 12 Sixty-two year-old female patient with weight loss and low-grade night fever. Unenhanced abdominal CT shows bilateral adrenal masses 12 cm in anteroposterior diameter, with a density of 38 HU (right) and 41 HU (left). FNAB was performed with suspected diagnosis of metastasis. Pathology revealed primary bilateral B-cell lymphoma.

Figure 13 (a) Patient with non-Hodgkin lymphoma and right adrenal nodule (asterisk). (b) Same patient after treatment (stars) show a decrease in size of thoracic, abdominal and adrenal lesion.
than secondary involvement and it is generally bilateral\textsuperscript{16} (fig. 12). In these cases, the adrenal function may be compromised, leading to acute adrenal insufficiency. Therefore, adrenal function should be evaluated by measuring blood cortisol levels at baseline and post-ACTH stimulation.

One third of patients with non-Hodgkin lymphoma have extranodal disease at the time of presentation, with the diffuse form being much more common than the nodular form. Adrenal lymphoma usually responds to treatment as other extraadrenal sites of disease (fig. 13). If there is no response to treatment of an adrenal mass in a patient with non-Hodgkin lymphoma, while there is a decrease in size the extraadrenal masses, a different pathology should be considered\textsuperscript{19}. According to the literature, 4\% of cases of non-Hodgkin lymphoma had a secondary adrenal involvement (43\% of these cases were bilateral). Twenty-five percent of patients with non-Hodgkin lymphoma has had adrenal involvement at autopsy\textsuperscript{59,60}. Primary and secondary lymphomas are hypermetabolic. For this reason, FDG-PET/CT is very useful for diagnosis, staging and assessment of treatment response of these tumors.

**Metastases**

It is important to recognize the appearance and size of adrenal glands when imaging cancer patients. The primary tumors that most often metastasize to the adrenal gland are lung, breast and stomach cancer, melanoma and lymphoma. Patients with lymphoma, colorectal, stomach or prostate cancer may develop adrenal metastases up to 5 years after diagnosis of their primary tumor\textsuperscript{19}. Fifty-six percent of secondary lesions are adenocarcinomas.
and 15% are squamous cell carcinomas. The remainder includes hematopoietic tumors, sarcomas and melanomas. In 50% of metastases are bilateral with an attenuation significantly higher than adenomas on unenhanced CT images (>30 HU). As regards wash out time, metastases demonstrate APW <60% and RPW < 40%\textsuperscript{19,23,25} and are found to have hypermetabolic adrenal activity by FDG-PET/CT with a higher standard uptake value (SUV) compared to the liver (fig. 14). Hypervascular metastases enhance similarly to pheochromocytomas, in particular metastases from renal cell carcinoma. In the setting of a known primary lesion, a decrease in the percentage washout at contrast-enhanced CT (APW < 60% and RPW < 40%), associated with a signal intensity equal to or higher than that of the spleen on MRI (out-of-phase chemical shift image), favors a diagnosis of metastasis (fig. 15). FDG-PET/CT is highly useful for detecting hypermetabolic metastases. False negative scans may occur in the presence of central necrosis, or with metastases smaller than one cm in size or metastasis from bronchioalveolar carcinoma, carcinoid tumors, mucinous tumors and renal cell carcinomas\textsuperscript{10,59,60}. We should bear in mind that 50% of adrenal lesions in patients with a primary tumor are benign; therefore, lesions should be accurately characterized prior to biopsy\textsuperscript{10} (fig. 16). FNAB should be performed only when metastasis is suspected (when clinical assessment and imaging findings are non conclusive or the primary tumor is of unknown origin), but it should not be performed when ACC is suspected, as this tumor reproduces the histological features of the gland, and therefore it is of no diagnostic value.

Figure 16 (a) Patient with non-Hodgkin lymphoma and left adrenal lesion (asterisk). (b) Same patient. FDG-PET/CT showed low hypermetabolic level of the adrenal lesion, similar to the liver. Follow-up revealed no growth of the lesion at 24 months. Diagnosis: nonfunctioning adrenal adenoma.

Conclusion

The small adrenal glands do not reflect their critical clinical relevance. Medical imaging plays a decisive role in the detection and characterization of adrenal disease. Currently available imaging techniques enable us to make a differential diagnosis between benign and malignant lesions. Furthermore, the value of interdisciplinary work should be emphasized, since the contribution of endocrinologists and biochemical assessments are essential to determine the functioning or nonfunctioning nature of a lesion. The use of an appropriate diagnostic algorithm enables a proper characterization of adrenal lesions in the shortest possible time. It also reduces radiation exposure and avoids unnecessary studies, thus leading to optimization of resources and better treatment planning.

Conflicts of interest

The authors declare no conflicts of interest, except for Dr. Binda who declares a possible conflict of interest as associate editor of RAR.

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