# Adrenal ganglioneuroma

*Ganglioneuroma de adrenal*

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## SUMÁRIO

Incidentalomas adrenais (IA) são massas descobertas ao acaso na investigação de distúrbios não relacionados a patologias das glândulas adrenais e tem se tornado cada vez mais frequentes. A maioria dos casos é constituída por adenomas não secretores, embora possa também representar uma neoplasia maligna primária ou metastática. Porém, no diagnóstico diferencial, doenças menos prevalentes não podem ser esquecidas. Relatamos um caso de massa adrenal em mulher jovem, sem sinais de hiperfunção clínica ou laboratorial. O diagnóstico foi feito após episódio de pielonefrite aguda, em que o exame de imagem foi realizado para excluir complicações locais. Durante a abordagem cirúrgica, o aspecto em carne de peixe da lesão fez suscitar a hipótese de uma lesão de origem neural, a qual foi prontamente definida pelo exame histopatológico. A paciente se apresentava com a manifestação mais comum do ganglioneuroma de adrenal, um incidentaloma. Arq Bras Endocrinol Metab. 2012;56(4):270-4

## SUMMARY

Adrenal incidentalomas (AI) are unsuspected adrenal masses discovered during investigation of unrelated diseases, and are increasing in frequency. The majority of the AI is non-secretory adenomas, although it can also represent primary or metastatic malignant neoplasia. However, less frequent diseases should not be forgotten in the differential diagnosis. We describe a case of a young woman with an adrenal mass without clinical or laboratorial signs of hormonal hyperfunction. Diagnosis was performed after an episode of acute pyelonephritis in which the imaging study was carried out in order to exclude local complications. During the surgical procedure, the fish flesh aspect of the mass raised the suspicion of a neurogenic tumor, which was diagnosed in the histophatological analysis. The patient presented the most common manifestation of adrenal ganglioneuroma, an incidentaloma. Arq Bras Endocrinol Metab. 2012;56(4):270-4

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## INTRODUCTION

Adrenal incidentalomas (AI) are masses discovered by chance in imaging investigations of disorders unrelated to adrenal disease. This unexpected diagnosis has become increasingly frequent and a common problem in clinical practice with increasing availability of high-resolution imaging procedures, such as computed tomography (CT) and magnetic resonance imaging (MRI) (1).

AI is uncommon below the age of 30 and its frequency increases progressively in adults and the elderly (2). The prevalence approaches 0.2% in young patients, 3% in people over 50 years of age, and reaches 7% in those over 70 years of age (1,2). In a Brazilian study (3), AI was found in 2.5% of patients undergoing chest and abdomen CT.

The vast majority of cases consists of non-secretory adrenocortical adenomas, although the disorder may also represent primary or metastatic malignancy neoplasm, or be manifested in the form of subclinical hyperfunction at diagnosis (1,4-6). However, as occurred the case reported here, less prevalent diseases should not be forgotten in differential diagnosis.

## CASE REPORT

A 21-year-old female without previous comorbidities, was admitted to a hospital with four days of evolution of high fever, dysuria, and back pain. Empiric treatment

for acute pyelonephritis was initiated after urine culture. Hours after admission, an ultrasound of the abdomen showed a heterogeneous, well-defined mass, measuring 12.2 x 7.6 x 7.8 cm, located near liver and right kidney.

After initiating the antibiotic therapy, without fever and improvement of laboratory results, the patient underwent a computed tomography of the abdomen and pelvis which showed of expansive mass (11 x 8.5 x 8.2 cm) with central thin calcifications and well-defined edges on the topography of the right adrenal. After pyelonephritis treatment, the patient was referred to the Service of Endocrinology, University Hospital Clementino Fraga Filho, Universidade Federal Rio de Janeiro (UFRJ--HUCFF) for further investigation of the adrenal mass.

In her past medical history, the patient denied comorbidities, as well as signs/symptoms of hypercortisolism and virilization, high blood pressure levels or paroxysms of headache, palpitations or sweating. She denied previously hospital admissions, except for a Caesarean section. Her periods were regular and she was a mother of a healthy 18-month-old baby girl (GI/PI/A0). She denied smoking, alcohol consumption and recent trips.

Physical examination upon admission at HUCFF was absolutely normal, except for the abdomen, where a hardened, undefined and painless mass was palpable in the right flank. The thyroid was normal at palpation. She had gynecoid distribution of hair, and no violaceous striae.

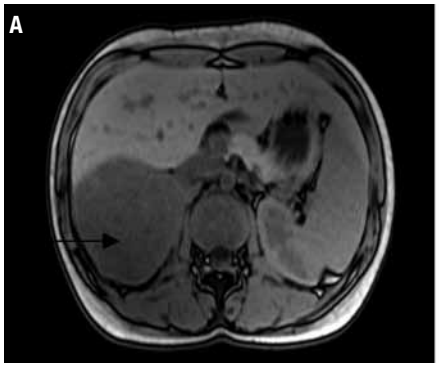
During hospitalization at the HUCFF, the study was complemented with laboratory examination, which showed no changes; and magnetic resonance imaging (MRI) of the abdomen (Figure 1). The MRI revealed the presence of a large expansive heterogeneous formation measuring about 9.0 x 7.5 x 7.7 cm, located in the topography of the right adrenal.

The investigation was negative for Cushing's syndrome and subclinical pheochromocytoma (Table 1). Primary aldosteronism was not investigated due to the absence of hypertension.

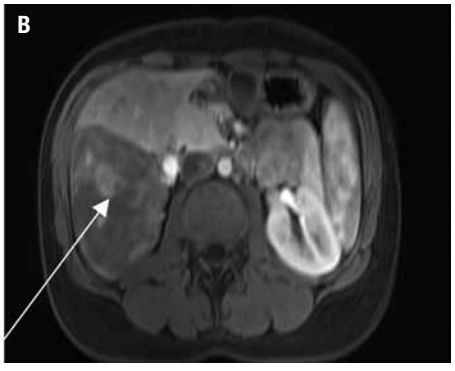
Surgery was indicated for a higher diagnostic accuracy.

## DIAGNOSIS

The patient underwent an exploratory laparotomy with right adrenalectomy without complications (Figure 2). The frozen biopsy raised the suspicion of either ganglioneuroma or anomalous sympathetic ganglion due to retrocaval injury. The histopathological report showed that right adrenal weighed 475 g, and measured 15.5 x 8.5 x 7.5 cm. The surface was light brown, sometimes covered by a thin transparent capsule, sometimes with attached membranous and adipose tissue of 10 x 5 cm. The sections were light brown, with a fleshy appearance, showing nodules with gelatinous areas. A cystic area of 3 x 2 cm was observed. Glandular tissue of usual aspect and measuring 2 x 7.5 x 0.2 cm was observed in the gap between this area and the lesion. Final diagnosis was adrenal ganglioneuroma, mature type (Figure 3).

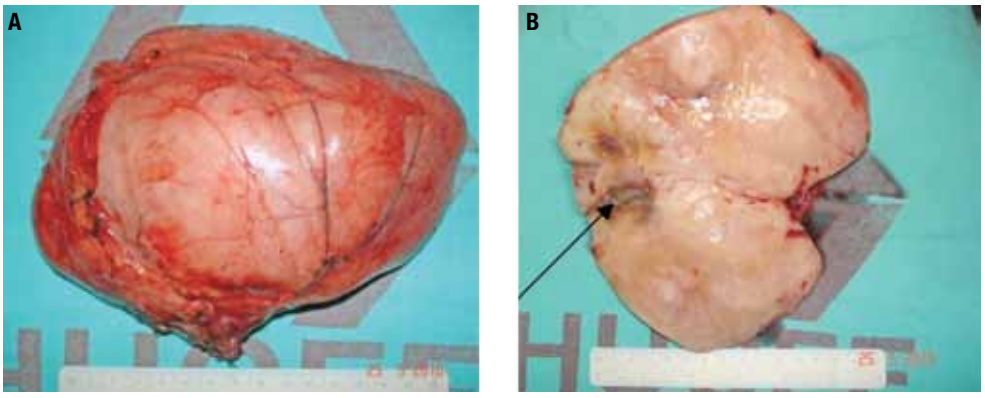



The arrow points to the damage repel liver anteriorly and kidney inferiorly.




The arrow points to the voluminous expansive formation with heterogeneous uptake of the contrast media.

**Figure 1.** Picture of T1 MRI of the abdomen before (A) and after (B) contrast: large expansive heterogeneous formation measuring about 9.0 x 7.5 x 7.7 cm, located in the topography of the right adrenal, with predominantly hypointense signal on T1-weighted sequences, hypertense signal on T2-weighted sequences, and heterogeneous uptake of the contrast media, restricted diffusion, as well as cystic areas/necrosis. The tumor previously rejected the liver, without well-defined cleavage plane with this organ, and the kidney moved inferiorly on this side.




Light-brown surface, sometimes covered by a thin transparent capsule, sometimes with adhered adipose and membranous tissue.

Light brown appearance, fleshy appearance, showing areas with gelatinous nodules (arrow).

**Figure 2.** Picture of the specimen in anatomical position (A) and sagittal section (B). Right adrenal with 475 g, measuring 15.5 x 8.5 x 7.5 cm. A cystic area of 3.0 x 2.0 cm was observed.

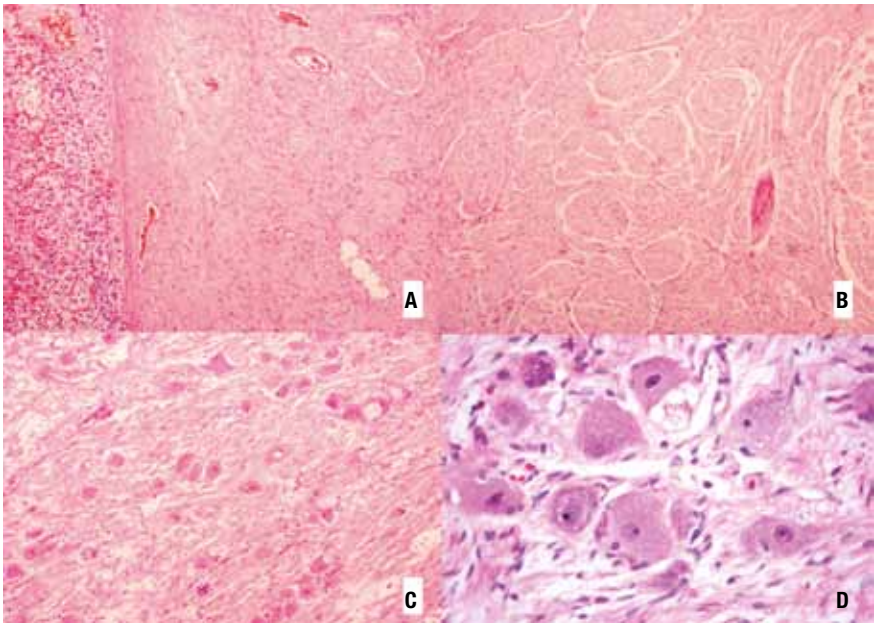



**Figure 3.** Microscopical view of adrenal tissue stained by hematoxylin and eosin (HE). (A) HE 10x – adrenal next to the tumor; (B) HE 40x – pattern of nerve bundles in the neoplasm; (C) HE 40x – diffuse fusiform pattern with interposed ganglion cells; (D) HE 40x – ganglion cells in detail.

**Table 1.** Results of hormone tests for pheochromocytoma and Cushing's syndrome

| Tests | Result | Reference range | Unit |
|---|---|---|---|
| 1-mg overnight Dexamethasone suppression test | < 1 | < 1.8 | µg/dL |
| Urinary catecholamines Norepinephrine | 58.2 | < 200 | µg/24 h |
| Urinary catecholamines Epinephrine | 7.1 | < 60 | µg/24 h |
| Urinary catecholamines Dopamine | 339.7 | 65-400 | µg/24 h |
| Urinary metanephrines Total | 148.8 | < 1000 | µg/24 h |
| Urinary metanephrines Metanephrine | 15.2 | < 400 | µg/24 h |
| Urinary metanephrines Normetanephrine | 133.6 | < 600 | µg/24 h |

## DISCUSSION

We report the case of an adrenal bulging mass without signs of clinical or laboratory hyperfunction. Differential diagnoses include nonfunctioning adenoma, for its high prevalence, even if it does not present the classical radiological aspect, and even adrenal carcinoma, because of its massive size. However, a large number of diagnostic hypotheses is possible (Table 2).

**Table 2.** Causes of adrenal mass

| |
|---|
| Functioning: > 15% |
| Adenoma (aldosterone or cortisol) |
| Carcinoma |
| Pheochromocytoma |
| Congenital adrenal hyperplasia* |
| Macronodular or micronodular adrenal disease* |
| Nonfunctioning |
| Adenoma |
| Myelolipoma |
| Neuroblastoma/ganglioneuroma |
| Hemangioma |
| Metastases* |
| Cyst |
| Bleeding* |
| Granuloma* |
| Amyloidosis* |
| Infiltrative diseases* |

* Bilateral involvement.
Adapted from Nieman LK. Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab. 2010;95(9):4106-13.

The patient described in this case presented the most common manifestation of adrenal ganglioneuroma, an incidentaloma. The mass was diagnosed after an episode of acute pyelonephritis, in which the imaging study was done to exclude local complications and compression. It is even possible that the retroperitoneal mass had some implications in the onset of the kidney infection by compressing the genitourinary tract.

Adrenal incidentalomas are uncommon in patients younger than 30 years of age, but increase in frequency with age. It affects men and women equally. In more than 85% of cases, lesions are benign nonfunctioning adenomas. Functioning tumors and carcinomas are not generally incidentalomas, since their diagnosis is based on specific signs and symptoms. However, some functioning tumors may present a subclinical form (Cushing's adrenal in 20% of the cases and pheochromocytoma) without specific symptoms. Thus, all patients with adrenal incidentaloma should be evaluated with hormonal screening tests. Cushing's syndrome (urinary free cortisol, late-night salivary cortisol, and 1-mg overnight dexamethasone suppression test) and pheochromocytoma (urinary catecholamines and metanephrines) should always be excluded. If there is hypertension, screening for primary hyperaldosteronism is also mandatory (plasma aldosterone/renin ratio). SDHEA dosage is also recommended by some authors, since it is a marker of adrenal androgen secretion.

Adrenal carcinoma is rare, especially in patients who have no history of malignancy. The size seems to be a strong predictor of malignancy, and a lesion smaller than 4.5 cm is considered at low risk for malignancy. These patients can be followed up with annual abdominal CT and hormonal tests. However, there is no consensus on how to follow up non-surgical patients. For masses that seem to be benign in the imaging study (< 10 Hounsfield Units – HU; contrast washout > 50%), small (< 3 cm) and nonfunctioning, biochemical and imaging revaluation can be done every 1 to 2 years, and later assessment if clinical changes. For indeterminate masses, it is prudent to perform imaging tests again in three months to one year to assess growth (7). Many authors recommend annual screening for Cushing's syndrome and pheochromocytoma over a period of four years. However, this strategy does not appear to be cost-effective (8). Even lesions larger than 5 cm are more likely to be benign than malignant, but due to the increased risk of malignancy, most centers recommend a surgical approach (9). Other features on CT or MRI, such as heterogeneity, irregular edges, increased density (> 20 HU), and low contrast washout (7,10) may indicate surgery regardless of size.

The fish flesh appearance of the tumor raised the hipothesis of an injury of neural origin, which was confirmed by histopathology. Ganglioneuroma is a benign neoplasm that arises from neural crest cells of sympathetic ganglia or adrenal medulla. It represents the most well-differentiated tumor in the neuroblastoma--ganglioneuroblastoma-ganglioneuroma spectrum, and may be primary or differenciate from a neuroblastoma or ganglioneuroblastoma (11). It occurs more often in adults between the ages of 40-50 years. The main locations are the posterior mediastinum, retroperitoneum, adrenal gland, and neck. Twenty percent of the ganglioneuromas are located in the adrenal medulla. The characteristics in the histopathological examination are mature ganglion cells and Schwann cells among a fibrous stroma.

At imaging studies, it appears as a relatively homogeneous, encapsulated mass, with well-defined edges and without invading nearby structures. Calcification occurs in 40%-60% of cases (12). Just as in cases of pheochromocytoma, they can have a strong/bright T2 signal (13). The 18F-labeled fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) may help distinguish between adrenal carcinoma and ganglioneuroma, based on the lowest standard uptake value, when compared to adrenal carcinoma (14). The main features of adrenal ganglioneuroma are summarized in table 3.

**Table 3.** Main characteristics of adrenal ganglioneuromas

| | |
|---|---|
| Clinical | Incidentaloma/compressive symptoms may occur |
| Radiology | Homogeneous, encapsulated mass, with well-defined edges and without invasion of nearby structures/calcification (40%-60%)/intense signal on T2-bright |
| Laboratory | Nonfunctioning/Rare: secretion of catecholamines, vasoactive polypeptides and androgens |
| Microscopy | Mature ganglion cells and Schwann cells among a fibrous stroma |

Although they are not metabolically active, there may be an increase in catecholamine secretion and uptake of metaiodobenzylguanidine (57%) (15), and this fact is related to the degree of the immaturity of the tumor.

Clinically, the majority of these tumors is asymptomatic and hormonally non-secretory (incidentalomas). However, in some cases, secretion of catecholamines, vasoactive polypeptides and androgens have been described (in association with pheochromocytomas) (14). Compressive symptoms may occur. The prognosis is very good with surgical removal (11).

There has only been 41 cases reported in the literature in English from 1961 to 2009, 22 involving women and 19 involving men, with a mean age of 44 years and with incidentaloma as the initial presentation.

Therefore, we present here a rare case in the literature of a benign tumor of neural origin of the adrenal medulla, which is most often presented as an incidentaloma or by compressive symptoms. Surgery leads to definitive cure, most of the time.

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