

CASE REPORT

Functional plurihormonal adrenal oncocytoma: case report and literature review

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Key Clinical Message

We present a 27-year-old woman with an adrenal oncocytoma. This is a very rare entity. We provide a review of the clinical, biochemical and pathological features of cases reported in the literature.

Keywords

Adrenal gland, adrenal oncocytic carcinoma, adrenal oncocytic neoplasm, adrenal oncocytoma, oncocytoma.

Introduction

Oncocytomas or oncocytic neoplasms are composed of tumor cells that show abundant granular eosinophilic cytoplasm by microscopy, and which may adopt an alveolar, tubular, or solid pattern [1]. Ultrastructurally, granular cytoplasm is caused by massive accumulation of mitochondria [2].

The organs most commonly involved are the kidney, salivary glands, and thyroid gland. However, cases have been reported in parathyroid glands, pituitary gland, larynx, liver, breast, ovary, stomach, small intestine, thymus, prostate, and lung [1, 3–7].

When located in the retroperitoneum, oncocytic neoplasms may be either renal or adrenal in origin. Limited cases of retroperitoneal heterotopic adrenal oncocytomas have been reported [8–10].

Oncocytic neoplasms arising from the adrenal gland are rare: 1.8% of adrenal masses, predominantly affecting the adult population [11]. Most of these tumors involve the adrenocortical region, while oncocytic pheochromocytomas are extremely rare [12].

Since the first description of oncocytomas in 1986, confirmed by electron microscopy [13], approximately 147 cases have been reported in the literature [14], most of them described as adrenal incidentalomas. They have been traditionally considered as benign and nonfunctional tumors, although recent data suggest that 20% of oncocytomas show some elements of malignancy and 10–20% are functional [15].

According to their biologic behavior, oncocytomas are classified as malignant, borderline (or of uncertain malignant potential), and benign, based on the criteria proposed in 2004 by Bisceglia et al. [15]. This classification includes major criteria: venous invasion, presence of atypical mitoses, and a high mitotic rate (more than five mitoses per 50 high-power fields) and minor criteria: presence of necrosis, size >10 centimeters and weight >200 g, capsular invasion, or sinusoidal invasion. The presence of at least one major criterion indicates malignancy, while the presence of at least one minor criterion indicates uncertain malignant potential (borderline). The absence of major and minor criteria is indicative of benign oncocytoma.

As oncocytoma is a very rare entity, the aim of this article was to report a case of plurihormonal adrenal oncocytoma and to provide a review of the clinical, biochemical, and pathological features of cases reported in the literature.

Material and Methods

We present a case report and a systematic literature review of articles published over the 29-year period between 1986 and 2015. OVID MEDLINE and PubMed were used to identify relevant articles. The key words “oncocytoma,” “adrenal gland,” “adrenal oncocytoma,” “adrenal oncocytic neoplasm,” and “adrenal oncocytic carcinoma” were used. No language restrictions were imposed. Original articles, review articles, and editorials were included and reviewed in order to select relevant articles. A total of 115 articles were identified. Only full-text publications or abstracts containing a description of relevant clinical, biochemical, and pathological features were included. Six articles were excluded because the full text could not be obtained and the abstracts contained insufficient data. Data of 109 articles were included in the review, comprising 183 cases of oncocytoma. Data were collected on age, gender, form of presentation, symptoms, hormonal hyperfunction, size, weight, biologic behavior, and progress.

Case Report

A twenty-seven-year-old woman with no relevant medical history presented with lower back pain of one-year duration.

She denied any history of medications, smoking, hypertension, headaches, palpitations, excessive perspiration, muscle weakness, bruising easily, fatigue, hematuria, menstrual disorders, acne, or hirsutism.

Physical examination was unremarkable; specifically, no masses, lymphadenopathy, peripheral edema, hirsutism, acne, alopecia, cushingoid features, striae, or petechiae were noted. Blood pressure: 110/70 mmHg, with no orthostatic hypotension.

An ultrasound scan was performed because of the lower back pain and showed a 46 × 40-mm hypoechoic solid lesion in the left adrenal gland. A CT scan of the abdomen and pelvis was ordered, which demonstrated a 50 × 42-mm rounded, solid, homogeneous expansive lesion of distinct borders in the left adrenal gland. The lesion had a spontaneous density of 46 Hounsfield units, showing enhancement after contrast administration (Figs 1 and 2).

The patient's complete blood count, urine analysis, blood urea nitrogen, and creatinine levels were all within normal limits.

Laboratory tests were ordered during the early follicular phase, and at 8 AM fasting, the results were as follows:



Figure 1. CT scan showed a 50 × 42-mm rounded, solid, homogeneous expansive lesion of distinct borders in the left adrenal gland.



Figure 2. CT scan showed a slightly enhanced tumor in the left adrenal gland.

total testosterone: 0.9 ng/mL (normal: 0.1–0.8 ng/mL), DHEA-S: 2735.3 ng/mL (normal: 201–4142 ng/mL), androstenedione: 3.3 (normal: 0.5–2.7 ng/mL), 17 hydroxyprogesterone: 3.1 ng/mL (normal: 0.3–1.0 ng/mL), aldosterone: 11 ng/dL (normal: 1.2–16 ng/dL), plasma renin activity (PRA): 0.2 ng/mL/h (normal: 0.5–2.6 ng/mL/h), aldosterone/ARP ratio: 55, sodium: 141 mmol/L (normal: 135–145 mmol/L), potassium: 3.9 mmol/L (normal: 3.5–5.3 mmol/L), plasma cortisol: 16.2 μg/dL (normal: 5–25 μg/dL), and ACTH: <10.0 pg/mL (normal: <54 pg/mL). Other measurements were ordered, including salivary cortisol at 23:00 h: 9.3 nmol/L (normal: 0.7–5.0 nmol/L), urinary free cortisol: 73.2 μg/24 h (normal: <100.0 μg/24 h), adrenaline: 4.7 μg/24 h (normal: 0–6.2 μg/24 h), noradrenaline: 14.2 μg/24 h (normal: 11.3–74.3 μg/24 h), and vanillylmandelic acid:

3.8 mg/24 h (normal: <8.5 mg/24 h); 24-h urinary metanephrines measurement was not available in our country at the time of the patient evaluation.

Measurement of nocturnal salivary cortisol was repeated: 5.1 nmol/L (normal: 0.7–5.0 nmol/L). Overnight 1 mg dexamethasone suppression test was ordered: Plasma cortisol levels at 8 AM were 16.3 µg/dL (normal <1.8 µg/dL). Endogenous hypercortisolism of adrenal origin was confirmed, associated with biochemical features consistent with elevated aldosterone/PRA ratio (primary aldosteronism not evaluated by confirmatory tests) and hyperandrogenism.

Because of tumor size and plurihormonal secretion, a decision was made to proceed with surgery, which was performed 10 months after diagnosis. A laparoscopic approach was used, but because of the large tumor size, conversion to open surgery was necessary. Left adrenalectomy was performed. No preoperative therapy was performed because there were no clinical or biochemical data suggesting catecholamine hypersecretion; however, careful intraoperative blood pressure monitoring was performed, which remained stable throughout the procedure. The patient made good progress, receiving postoperative hydrocortisone replacement 20 mg/day for 2 months.

Pathology findings

Left adrenal gland that weighed 134 g and measured 9.9 × 7.5 × 4.9 cm, with a brownish surface. On cut section, the parenchyma was replaced by a brownish-yellowish tumor proliferation, with areas of hemorrhage and hard-elastic consistency. Histological sections revealed tumor proliferation composed of polygonal cells of large hyperchromatic bizarre nuclei with isolated intranuclear vacuoles and prominent nucleoli; abundant eosinophilic cytoplasm. Cells were arranged in nests separated by thin fibrous septae; the tumor mass was surrounded by a thick capsule. The mitotic index was low: 2–3 mitoses per 50 high-power fields. There was no evidence of vascular embolism or capsular invasion. Little residual adrenal parenchyma was observed at the periphery of the lesion. Ki-67: 3%.

Two months after surgery, hydrocortisone therapy was discontinued and hormonal laboratory measurements were performed, with normal results (Table 1).

The patient made good progress, with no evidence of tumor recurrence on the follow-up computed tomography scans and laboratory tests performed annually during the last 9 years.

Discussion

Among adrenal tumors, oncocytomas are a rare subtype. Most cases reported in the literature are isolated cases,

Table 1. Preoperative and postoperative hormonal laboratory measurements.

	Preoperative	Postoperative
Total testosterone (RR: 0.1–0.8 ng/mL)	0.9	<0.1
DHEA-S (RR: 201–4142 ng/mL)	2735.3	1075.0
Androstenedione (RR: 0.5–2.7 ng/mL)	3.3	1.2
17 hydroxyprogesterone (RR: 0.3–1.0 ng/mL)	3.1	0.5
Aldosterone (RR: 1.2–16 ng/dL)	11	14
PRA (RR: 0.5–2.6 ng/ml/h)	0.2	0.44
Aldosterone/PRA ratio	55	31.8
Plasma cortisol (RR: 5–25 µg%)	16.2	14.3
ACTH (RR: <54 pg/mL)	<10	29
Urinary free cortisol (RR: <100 µg/24 h)	73.2	18.0
Salivary cortisol at 23:00 h (RR: 0.7–5.0 nmol/L)	9.3	1.8

RR, reference range; DHEA-S, dehydroepiandrosterone sulfate; PRA, plasma renin activity; ACTH, adrenocorticotropic hormone. Blood samples were taken at 8:00 AM after 12-h nocturnal fasting. Aldosterone/PRA ratio was elevated, and not confirmatory test was performed.

with the largest series being that reported by Mearini *et al.*, with a total of 147 cases [14].

We have found 183 case reports of adrenal oncocytomas, from which we could collect clinical, biochemical, and histological data (data are presented as the mean ± SD). These tumors are more frequent in females (2/3) and may occur in all age groups, with a predominant occurrence approximately in the fourth and fifth decades of life (45.1 ± 15.9 years). In agreement with literature reports, about 20% were malignant (22.4%) and about 30% were functional (27.9%). As regards location, previous reviews report a higher frequency on the left side; in this review, 56.2% of tumors occurred on the left side, 38.9% on the right side, 0.6% were bilateral, and 4.3% were heterotopic: retroperitoneum [8–10], lumbar spine [17], and broad ligament [18]. Macroscopically, most of them are large, rounded, encapsulated, and well-circumscribed tumors. On cut section, they are yellow brownish; some may exhibit areas of hemorrhage or necrosis. Microscopically, they are composed of large eosinophilic and granular cytoplasm cells with a central pyknotic nucleus, with a solid, trabecular, tubular, or papillary growth pattern. The immunohistochemical pattern was difficult to establish because it had not been described in many of the reported cases; these tumors are generally positive for vimentin, melan-A, synaptophysin, and alpha-inhibin and negative for chromogranin.

There is consensus that the most important problem regarding adrenal oncocytomas concerns their biologic behavior [15]. Aside from obviously malignant cases (unresectable tumors with local invasion or distant

metastases), the biologic behavior and prognosis of adrenal tumors are difficult to predict. The tool used for adrenocortical tumors, Weiss score, where nine histologic features are evaluated [19], is not useful because the features that are distinctive of oncocytic tumors (<25% clear cells, nuclear atypia, and diffuse architecture) encompass three criteria of the total; therefore, all oncocytomas would automatically reach the score to be classified as malignant, which is inconsistent with the benign progression observed in the long-term follow-up of many reported cases. For this reason, in 2004, Bisceglia *et al.* at proposed new criteria, based on a modified Weiss score, for the classification of oncocytic adrenal tumors, suggesting major criteria: venous invasion, presence of atypical mitoses, and a high mitotic rate (more than five mitoses per 50 high-power fields) and minor criteria: presence of necrosis, size >10 centimeters and weight >200 g, capsular invasion, or sinusoidal invasion. The presence of at least one major criterion indicates malignancy, while the presence of at least one minor criterion indicates uncertain malignant potential (borderline). The absence of major and minor criteria is indicative of benign oncocytoma [15]. It is also important to consider the tumor-proliferating fraction evaluated by immunohistochemistry for Ki 67. Various authors agree that a value >5% characterizes malignancy, while for benign and borderline oncocytomas, a value range between 0 and 4% is reported [15, 20].

Table 2 describes the characteristics of the oncocytomas reported in the literature and the gender and age of patients. Tumors are classified according to their biologic behavior using the criteria proposed by Bisceglia *et al.* [15].

Benign oncocytomas constituted 38.3% of all reported cases and were characterized by an average size of 5 cm. In most cases, these tumors were detected incidentally, while in 18.5% of cases patients presented with abdominal pain [12, 21–25]. Other less frequent forms of presentation were hirsutism [12, 26–28], virilization [29], pseudoprecocious puberty [30], Cushing's syndrome [27, 31, 32], blood hypertension [33–35], fever [36], pain in lower limbs [16, 17], fatigue [37, 38], and feminization [39].

Oncocytomas of uncertain malignant potential (borderline) accounted for 39.3% of cases, with a larger size on average (11.6 cm). Most cases were incidental findings, while the rest presented with abdominal or lumbar pain (29.2%), virilization (6%) [40–42], Cushing's syndrome [43], blood hypertension [44, 45], weight loss, hematuria [46, 47], fever, or palpable mass in a lower proportion [48, 49].

As regards malignant oncocytomas (22.4%), the average size was 13 cm. In 21.9% of cases, diagnosis was performed by abdominal pain or palpable mass and in 21.9% of cases by excessive hormone secretion symptoms (36.8%). In 10 cases, there was evidence of metastasis [50–56], and in two cases, there was invasion into the inferior vena cava [57, 58], while seven cases presented tumor recurrence after resection [55, 56, 59, 60].

As regards imaging methods, in addition to tumor size, the appearance and behavior after contrast administration are important data for the differential diagnosis of adrenal masses. Lipid content, evaluated by CT or magnetic resonance imaging, is the most important parameter for differentiating adrenal adenomas from lesions with malignant behavior, such as adrenal carcinoma or metastases. The majority of adrenal adenomas present attenuation values of less than 10 HU on unenhanced CT, reflecting the abundant intracellular lipid content, while 30% present higher densities and are considered lipid-poor adenomas. The behavior of lesions after contrast administration allows differentiation of adenomatous lesions from malignant tumors, as the former show a rapid washout of contrast (greater than 50%) on delayed scans, while carcinomas or metastases enhance intensely and retain contrast for longer periods. Khan *et al.* described a series of benign and malignant adrenal oncocytomas, comparing them with various adrenal carcinomas as to size, values of attenuation on CT scan and behavior of contrast material. Benign oncocytomas were more frequently homogeneous, with no evidence of calcification or hemorrhage. The value of attenuation was greater than 10 HU, which is consistent with the histological feature of poor intracellular lipid content. However,

Table 2. Characteristics of oncocytomas according to their biologic behavior.

	Benign	Uncertain or Borderline	Malignant
Number	70 (38.3%)	72 (39.3%)	41 (22.4%)
Age (years)	43.1 ± 16.7	44.9 ± 15.4	48.7 ± 15.1
Gender M/F	16/54 (23%/77%)	29/44 (40%/60%)	19/22 (46%/54%)
Functional	26 (37.1%)	11 (15.1%)	14 (34.1%)
Size (cm)	5.1 ± 2.1	11.3 ± 4.7	13.0 ± 6.1
Weight (g)	61.4 ± 53.1	600.0 ± 556.6	940.0 ± 1544.9

these tumors demonstrated high-contrast washout percentages, behaving similarly to lipid-poor adenomas. Oncocytic carcinomas showed similar features to those found in adrenocortical carcinomas, including larger size, heterogeneity, and presence of necrosis. They showed high values of attenuation on unenhanced CT, 39 HU on average, together with a washout percentage <50% after contrast administration [61].

Independently of the size and features of adrenal masses, in all cases it is necessary to perform a thorough hormonal assessment to determine whether there are signs of adrenal hyperfunction. Recommended tests include measurement of plasma or urinary fractionated metanephrines, low-dose dexamethasone suppression test, measurement of ACTH, estradiol, androgens (DHEA-S, delta 4 androstenedione, 17 hydroxyprogesterone, and testosterone) aldosterone and plasma renin activity. In our review of the literature, approximately one-third of benign oncocytomas were functional, secreting androgen in six cases [28, 29, 37, 62, 63], androgens and cortisol in five cases [26, 27, 31, 32], cortisol in six cases [34, 63, 64], estradiol in two cases [30, 39], IL-6 in two cases [36, 38], aldosterone in four cases [34, 35, 55], and catecholamines in the remaining case [65]. Among borderline tumors or tumors of uncertain malignant potential, hormonal hypersecretion was found in 17% of cases: four androgen-secreting tumors [4, 41, 66], two corticosteroid-secreting tumors [43, 67], two catecholamine-secreting tumors [45, 68], one corticosteroid- and androgen-secreting tumor [69], one aldosterone-secreting tumor [70], and one 17-ketosteroids-secreting tumor [71]. Among malignant oncocytomas, 33.3% were functional, secreting androgen in four cases [55, 72], cortisol in seven cases [34, 55, 59], androgens and cortisol in one case [54], aldosterone and cortisol in one case [60], and estrogens in one case [55]. There were no data available on the progress of patients with cortisol-secreting tumors, regarding the presence of signs or symptoms of adrenal suppression after surgery.

As adrenal oncocytomas usually present as masses larger than 5 cm, adrenalectomy is the treatment of choice, generally by the open surgical approach, although recently the use of the laparoscopic technique has been increasingly reported in cases of encapsulated tumors. The laparoscopic approach reduces pain and the perioperative hospital stay; however, the indication of this technique in cases of larger or potentially malignant tumors remains controversial [14]. After resection, follow-up will depend on the histological features of the tumor, depending on whether it is benign, of uncertain malignant potential or malignant. There are no general recommendations, but imaging and laboratory follow-up is suggested for a minimum of 5 years for functional tumors [14].

Our patient presented with lumbar pain as the only clinical manifestation; therefore, it was not an incidentaloma. Although the laboratory findings demonstrated a functional tumor, there were no clinical signs of adrenal hyperfunction. The hormonal evaluation showed ACTH-independent cortisol secretion and androgen secretion, which returned to normal levels in postoperative laboratory tests. Our patient received short-term hydrocortisone replacement therapy, with no clinical manifestations of adrenal suppression secondary to resection of the cortisol-secreting tumor. In most studies that evaluated patients with hyperaldosteronism, an aldosterone/PRA ratio >20 is considered highly suspicious for primary aldosteronism. An aldosterone/PRA ratio >30, especially in the setting of plasma aldosterone concentration ≥ 15 ng/dL, has been shown to be 90% sensitive and 91% specific for the diagnosis [73, 74]. Although the aldosterone/PRA ratio was high in our patient, no confirmatory tests were performed to establish the diagnosis of primary aldosteronism. There is a discrepancy between the size of the resected tumor and that reported in preoperative imaging assessments (by ultrasound and tomography). This might be possibly explained by a rapid tumor growth in the months between diagnosis and resection. However, histopathologically, none of the major or minor criteria proposed by Bisceglia [15] were observed; therefore, contrary to any expectations based on tumor growth rate, our case was classified as a benign oncocytoma, which is consistent with the good progress shown by the patient in the long-term follow-up.

In conclusion, adrenal oncocytic tumors are rare entities with a variable biologic behavior, which require a thorough hormonal evaluation for ruling out hyperfunction before surgical resection and for an adequate management in cases of cortisol-secreting tumors that may cause postoperative contralateral adrenal suppression. The pathologic examination must be performed by experienced pathologists in order to be able to classify tumors according to their biologic potential and to establish the patient's prognosis.

Authorship

PRC: contributed to patient evaluation, design and conduction of research, data acquisition and analysis, and drafting of the manuscript. ALP: helped in design and conduction of research, data acquisition and analysis, and drafting of the manuscript. PK: contributed to analysis of the data, drafting, and critical review of the manuscript.

Conflict of Interest

None declared.

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