

Case Report

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# Functional Adrenocortical Oncocytoma Presenting with Hyperandrogenism and Seizures

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## Abstract

A 38-year-old woman was referred to an Endocrinologist with sudden onset of a variety of clinical symptoms- epileptic seizures, amenorrhea, weight gain, hirsutism and sexual dysfunction. Her physical examination and biochemical investigations, including blood sugar were normal. Blood pressure was 110/80 mmHg. A right adrenal tumor was detected on ultrasonography and computed tomography. Blood levels of dehydroepiandrosteronesulphate, testosterone and aldosterone were increased 2.2, 7.6 and 1.6 times higher than maximal normal values respectively. The aldosterone/renin ratio was 176. The laparoscopic excised tumors of the right adrenal gland weighed 137 g and was red-yellowish-brown with the intact capsule. Histology of the tumor showed round, oval or polygonal cells with abundant granular eosinophilic cytoplasm. Nuclei were oval, basophilic and with nucleoli. Focally pleomorphic nuclei were noticed. The cells formed nests and trabeculae. Histological picture was suggestive for oncocytoma. Immunohistochemical investigations showed: alpha-inhibin-diffusely positive in tumor cells, synaptophysin-positive in zones of tumor cells, melan A-diffusely positive in tumor cells, Ki-67-positive in 10% of tumor cells, Chromogranin-negative in tumor cells but positive in medullary zone. After the surgery, almost all the hormones returned to normal and were maintained at this level for 12 months post operation. An exception was aldosterone, which was increased, but without symptoms of hyperaldosteronism. The patient did not report any seizures after the surgical treatment. Sexual function regained 6-12 months post-surgery.

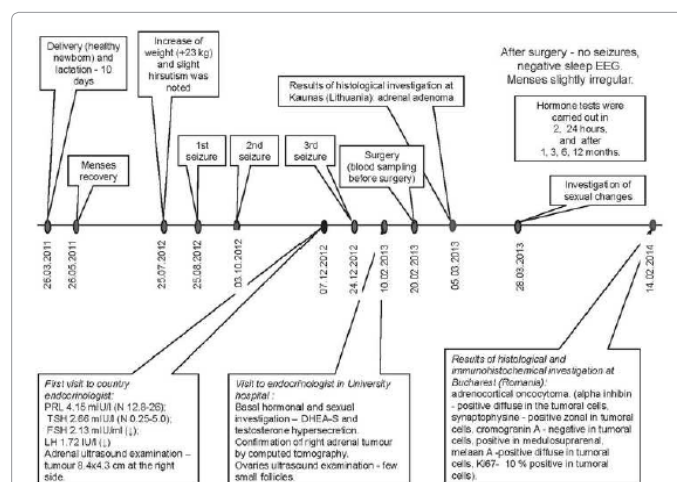
**Keywords:** Oncocytoma; Immunohistochemistry; Dehydroepiandrosterone sulfate; Testosterone; Subclinical hyperaldosteronism; Seizures

## Background

Adrenal oncocytoma is a rare neoplasm (about 150 cases reported), usually benign (about 80%) and rarely secretory (about 20%) [1]. The term oncocytoma refers to a tumor predominantly or exclusively composed of oncocytes which are characterized by large polygonal cells with abundant eosinophilic and granular cytoplasm [2,3]. Ultrastructurally, oncocytes are distinguished by the abnormal accumulation of densely packed mitochondria [4]. In addition to the adrenal gland, oncocytomas are described in various sites, including kidney, salivary gland, thyroid, parathyroid, pituitary, thymus, bronchus, lacrimal gland, breast, liver, ovary, stomach, small intestine and prostate [3,4]. Uncertainty exists regarding the natural history and clinical behavior of these tumors. Herein we present a female with adrenal oncocytoma identified by histological and immunohistochemical investigations, manifesting signs of hypersecretion of 3 dehydroepiandrosterone sulfate (DHEA-S), testosterone (T), and aldosterone (A) as well as stigmata consistent with a functioning tumor during the course of her disease.

## Case Presentation

A 38 year-old Caucasian female presented for evaluation of amenorrhea lasting 8 months, weight gain (23 kg in 6 months), hirsutism and 3 generalized tonic clonic seizures occurring in August, October and December 2012. We present a diagram with the evolution of the patient case (Figure 1). Awake and sleep electroencephalogram (EEG) did not register any abnormality. Magnetic resonance imaging of the brain was also normal. She underwent a right upper quadrant ultrasound with the discovery of a mass in the superior aspect of the right kidney. Computed tomography of the abdomen confirmed the presence of the mass localized in the right adrenal gland measuring 5.8 × 4.6 cm. It was described as an oval with homogeneous content and well-defined margins and suspected to be pheochromocytoma



**Figure 1:** Diagram of patient evolution, tumour, and histological aspects and immunohistochemistry of the adrenocortical oncocytoma.

by the radiologist prasideda mazaja raide, o ne didziaja. Her blood pressure was normal (110/80 mmHg). Before and after the surgery the patient did not receive any hormonal treatment. Basal biochemical

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investigations, including blood sugar were normal. Initially luteinizing hormone and follicle-stimulating hormone was decreased (resulting in secondary hypogonadotropic amenorrhea). Prolactin, metanephrine, normetanephrine, renin, cortisol, adrenocorticotrophic hormone and estradiol were normal with A and 17-OH progesterone slightly increased. T was very high (20.6 nmol/l, normal-up to 2.7) and DHEA-S was high (25.5 mcmol/l, normal-up to 11.5). A was high-706 pmol/l, renin- normal-4.0 ng/l, and aldosterone/renin ratio (ARR) high-176. Given the size of tumor and high blood level of DHEA-S and T, it was considered that the tumor was malignant, so the patient underwent a laparoscopic right adrenalectomy. The resected tumor was 11 cm diameter, weighed 137 g and was red-yellowish-brown in color with an intact capsule. On microscopy, the tumor was uniform in appearance and composed of round, oval or polygonal cells with abundant granular eosinophilic cytoplasm. The nuclei were oval and basophilic with nucleoli. Focally pleomorphic nuclei were noticed. The cells formed nests and trabeculae. A few areas of hemorrhage and infarction were noticed. Final pathological interpretation was consistent with an adrenocortical oncocytoma (Figure 2). 4 Immunohistochemistry revealed alpha inhibin-diffusely positive tumoral cells, synaptophysin-positive in tumoral cells, melan A-diffusely positive in tumoral cells and positive in the adrenals, and Ki 67-positive in 10% of tumoral cells (Figure 3). Chromogranin was negative in tumoral cells, but positive in the adrenal medulla (not shown). A significant decrease in DHEA-S and T appeared 2 hours after the surgery and became low after 24 hours (DHEA-S  $6.6 \pm 1.1$  mcmol/l and T  $9.96 \pm 1.11$  nmol/l). At the same time estradiol, A, renin, metanephrine, normethanephrine, 17-OH progesterone, adrenocorticotrophic hormone and cortisol levels were also decreased, later even to the level of adrenal insufficiency. Hormones recovered to normal values within 1 month, and remained in the normal range 12 months after surgery. The concentration of A was slightly increased before the surgery and decreased immediately afterwards, however, it remained slightly elevated 1, 3 and 12 months after the surgery without signs of primary hyperaldosteronism. The patient recovered well and did not receive any adjuvant therapy apart from close observation and follow up. Her menstrual cycle restored spontaneously in 6 weeks and hot flashes ceased. Seizures did not appear during the 12 months after the surgery. Sexual function was assessed using the validated Female Sexual Function Index [5]. The score 1 month before the operation was 19/36 and 1 month after the operation 25/36. Maximum sexual function was achieved 12 months post-surgery at 33/36.

## Discussion

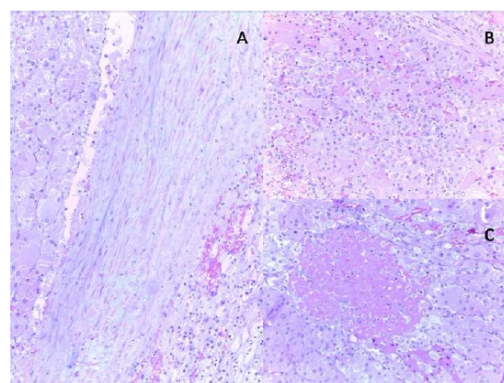
### Benign secretory adrenocortical oncocytoma

The adrenal tumor described here complies with the criteria for a benign secretory adrenal oncocytoma. Adrenocortical oncocytomas are extremely rare adrenal neoplasms with just 147 cases cited in the literature (by 2013) with only 17 % secretory [1]. None of these patients had seizures. The tumors had variable size at presentation (3 to 20 cm) with a female-to-male predominance of 2.5:1 and a strong left-to-right sided prevalence of 3.5:1 [2]. Microscopically the tumor was a large, rounded, encapsulated and well-circumscribed mass, with only a small area of intact adrenal left at the periphery. Histologically, it was composed of nests and trabeculae of oncocytic cells. According to the Weiss criteria [6], it is a pure and benign oncocytoma. Only a few secretory adrenocortical oncocytomas are described. As a rule, DHEA-S and T secretions are increased [7,8]. Sometimes cortisol is co-produced [8], and there was one case described of an interleukin-6 secreting oncocytoma [9]. Although each clinical picture was different, one or

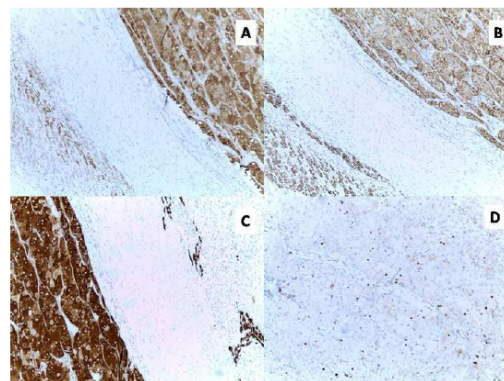
more clinical manifestation of hyperandrogenism was reported. No epileptic seizures were described in cases with high endogenous levels of DHEA-S. In our patient the disappearance of epileptic seizures after removal of the DHEA-S and T secreting tumor support the affirmation that seizures were provoked by hypersecretion of these hormones.

### Morphological and immunohistochemical differentiation between adrenal adenoma and oncocytoma

Since 1998, Melan A and alpha-inhibin have become the most commonly used markers to confirm the adrenal cortical origin of a given lesion [10-12]. Alpha-inhibin has also been shown to reflect the hormonal secretion of the tumor, being more frequently and intensively expressed in androgen - secreting neoplasms [13]. Our investigation has demonstrated melan A-to be diffusely positive in tumoral cells and positive in the adrenals (Figure 2), thus proving the adrenal cortical origin of the tumor. It is important to distinguish between benign and malignant characteristics of tumor cells and to date, the proliferation marker Ki-67 is the sole immunohistochemical antibody shown to be useful in the differential diagnosis between adenoma and carcinoma [14-17]. The Ki-67 proliferation index has been investigated as a prognostic marker for several years [18,19]. In a 6 recent study Ki-67



**Figure 2:** Histological aspects of the adrenocortical oncocytoma: A. Tumour nodular proliferation within encapsulated adrenal. Round, oval or polygonal cells with an abundant cytoplasm, slightly granular, eosinophilic and sometimes with vacuolization. Nucleus oval, basophilic with nucleoli, in some places nuclear pleomorphism was present. Disposition in nests and trabeculae sometimes with necrotic areas. Haemorrhages sometimes detectable; B. Nuclei bizarre, atypical; C. Area of necrosis.



**Figure 3:** Immunohistochemistry of the adrenocortical oncocytoma: A. Alpha inhibin positive in the tumour cells (right) and positive in the rest of adrenal gland; B. Synaptophysin-positive in tumour cells (left) and in the rest of the adrenal gland (right); C. Melan A- tumour cells (right, up) and the rest of the adrenal gland (left, down); D. Ki-67 positive in 10% of tumour cells.

index proved to be superior to mitotic count in terms of the prognosis of adrenal cortical carcinoma, at least with regard to overall survival. Three subgroups of patients have been stratified based on cutoffs of <20, 20-50, and >50% [20]. We found the Ki-67 index to be positive in 10% of tumoral cells. Thus, according to this data our patient falls into the most favorable group regarding overall survival. Indeed, one year following surgery the patient remains in good health and presents no signs of disease relapse.

### Sudden DHEA-S and T decrease, causing transient menopausal symptoms.

The onset of transient menopausal symptoms such as weakness and hot flashes is most probably explained by the sudden elimination of T as an estradiol provider for the brain. *DHEA-S as proconvulsant neurosteroid*. A recent review by Reddy [21] proposed that the sulfated neurosteroids (Pregnenolone sulfate and DHEA-S) are excitatory and produce memory-enhancing and anxiogenic effects as well as proconvulsants and contributing to neurogenesis and neuroprotection. To our knowledge this is the first patient with a high level of endogenous DHEA-S and testosterone-provoked seizures, which resolved after extirpation of the source of these elevated hormones – the adrenocortical oncocytoma. We hypothesize that the extremely high and longstanding concentrations of endogenous DHEA-S in combination with some as yet unknown brain molecule provokes the clinical manifestation of epileptic seizures. The implication of sex hormones in the treatment of women with epilepsy has recently been reviewed [22].

### Changes in Aldosterone (A) secretion

Only 2 cases of oncocytomas secreting A, are described [23,24]. In our case A decreased to normal sometime after the surgery, but later tended to increase steadily, without other signs of hyperaldosteronism. Repeat computed tomography scan of the adrenal region did not reveal any pathology. Hypothetically, nests of A secreting cells are present in the adrenals. Excision of the main source of A secretion-adrenal oncocytoma-leads to a decrease in A during the first day after the operation. Remnant cellular nests, secreting A in the contralateral adrenal or the residual operated adrenal induce a slow increase of A secretion, but insufficient to provoke a clear clinical picture of primary hyperaldosteronism. Our theory concerning A hypersecretion would be supported by other articles describing atypical [25,26] and subclinical [27] primary aldosteronism without detectable tumors or hyperplasia on computed tomography scan. Also more sensitive imaging techniques (NP-59 SPECT/CT) now permit increasingly accurate diagnoses of adrenal A secreting tumors [28].

### Changes in sexual function

The sexual dysfunction of this patient raises some unexpected questions. Our clinical case showed that an adrenal gland tumor that is producing sex hormones has a negative impact on female sexual function. These findings are contradictory to the generally accepted hypothesis that androgens have a positive effect on female sexual function. Weight gain, hirsutism and psychological factors play a role in female sexual desire, but down-regulation of androgen receptors should not be disregarded as a causal factor.

### Conclusion

A case is described of immunohistochemical and histological aspects of a DHEA-S, testosterone and aldosterone secreting adrenocortical oncocytoma with multiple clinical symptoms. The hypersecretion of DHEA-S and testosterone are strongly suggestive as the etiological

factor for the amenorrhea, weight gain, hirsutism, seizures and sexual dysfunction. Persistent hypersecretion of aldosterone after removal of the adrenal oncocytoma suggest the presence of subclinical primary hyperaldosteronism.

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