



## Pure Androgen Secreting Unilateral Adrenal Hyperplasia with Contralateral Adenoma - Case Report and Literature Review

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### Abstract

Pure androgen-secreting adrenal tumors are extremely rare. We herewith present the case of a 47-years-old female patient who experienced hirsutism and amenorrhea for five years, intensified in the last year adding clitoromegaly, alopecia, increased muscle mass, and voice deepening. The biochemistry showed elevated serum total testosterone and DHEA-S. The computerized abdominal tomography showed a solid, nodular right adrenal mass deemed uncharacterizable, and an adenoma was reported on the left adrenal gland. A PET study showed low and diffuse metabolism in the right lesion and confirmed the left adenoma. The right-side adrenalectomy was performed by a laparoscopic approach. Signs and symptoms of hyperandrogenism and virilization subsided almost entirely, with decreased total testosterone and DHEA-S levels. The diagnosis is upon clinical suspicion with signs of hyperandrogenism and virilization, elevated serum androgen levels, and imaging evidence of adrenal tissue injury. However, all these are not enough for an accurate diagnosis, being the pathology report of foremost importance for the definitive diagnosis.

**Keywords:** Adrenal tumor, Adrenalectomy, Hirsutism, Hyperandrogenism, Virilization

### Introduction

Pure Androgen-Secreting Adrenal Tumors (PASATs) are sporadic and are often confused in clinical practice with adrenocortical carcinomas. Eighty percent occur in females and present with hirsutism, menstrual disorders, and virilization [1]. The following is a clinical case of PASAT in a 47-year-old woman, and a bibliographic search was carried out to update the evidence.

### Case Presentation

A 47-year-old female patient with no relevant background presents with a history of 5 years of hirsutism and amenorrhea, intensified in the previous year, adding alopecia, increased muscle mass, and voice deepening (Figure 1a, 1b). The physical examination reports an average weight, normal blood pressure, moderate hirsutism (18 on the Ferriman-Gallwey scoring system), and clitoromegaly without elements of Cushing's syndrome nor acanthosis nigricans syndrome.

Laboratory tests highlight the value of Total Testosterone of 937 ng/dl (reference value 8.4 to 48.1); serum Dehydroepiandrosterone sulfate (DHEA-S) 331 µg/dl (reference value 56.2 to 282.9); normal serum Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Prolactin (PRL); finally, a serum cortisol level of 1.6 µg/dl was obtained after a dexamethasone suppression test.

### Imaging

An abdominal Computed Tomography (CT) shows a solid nodular right adrenal mass with hypodense areas inside, 40x34x32 mm, washout of 16.3%, deemed uncharacterizable. On the left adrenal, an adenoma of 12 × 10 × 10 mm size is reported (Figure 2). A Positron Emission Tomography (PET-CT) with 18F-FDG (fluorine-18 fluorodeoxyglucose) shows low and diffuse metabolism in the right lesion and confirms the left adenoma (Figure 3).

### Pathology

Given the described findings, right-side adrenalectomy by the laparoscopic approach was decided and performed without complications. Multiple pathologists analyzed the histological

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Figures 1A and 1B: Patient's physical features relevant to the diagnosis.

**Table 1:** Weiss Score. Presence of 3 or more items is related to malignancy (specificity 96%, sensitivity 100%).

Weiss Histopathological scoring system
Nuclear grade (III or IV)
Mitotic rate: >5 for 50 fields (x400 objective)
Atypical mitotic figures
Cytoplasm ≤ 25% clear or vacuolated cells
Diffuse architecture >33% surface
Confluent necrosis
Venous invasion
Sinusoidal invasion
Invasion of tumor capsule

sample due to diagnostic doubts, and two possible etiologies were posed, nodular hyperplasia vs. cortical adenoma, without malignancy elements.

### Postoperative outcomes

In the follow-up visit two months after surgery, the signs and symptoms of hyperandrogenism and virilization decreased almost entirely. The total testosterone and DHEAS levels dropped to a normal range for age and sex regarding laboratory findings.

## Discussion

### Epidemiology

Virilizing adrenocortical tumors are rare in adults. About 50% appear before puberty, 39% correspond to adenomas, and 80% are seen in women. They have a high chance of malignancy (70%) if virilization appears in adult women, with rapidly progressive symptoms and Cushing syndrome. This association was ruled out in our patient [2].

According to Moreno et al. [3], PASATs make up for 2.4% of all adrenalectomies and cause 49% of women's virilizing syndromes. In their review of 34 patients with PASAT, Gabrilove et al. [4] report a slight predominance of the right adrenal compared to the left [4].

PASATs secrete DHEA and DHEA-S rather than testosterone. On the other hand, the predominance of testosterone tends the diagnosis towards an ovarian pathology [2]. It should be noted that there are no alterations found in the patient's ovaries. Exceptionally, there are adrenal tumors that secrete only testosterone in the absence of other androgens [2].



Figure 2: Abdominal CT. The continuous arrow indicates right adrenal lesion; the dashed arrow indicates left adrenal adenoma.

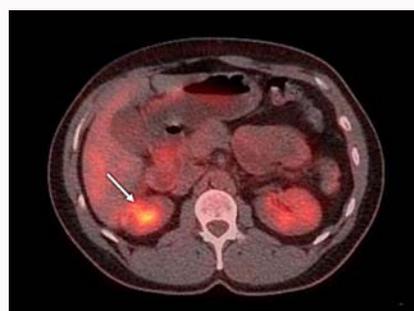


Figure 3: <sup>18</sup>F-FDG PET/CT. The arrow indicates the right adrenal lesion.

### Clinical findings

The androgen excess in women clinically shows with hirsutism and progress to virilization with clitoromegaly, voice deepening, alopecia, increase of muscle mass, changes in body fat distribution, and decrease in breast volume, among others. However, other entities present similar clinical manifestations, such as Polycystic Ovary Syndrome (PCOS), ovarian tumors, and congenital adrenal hyperplasia [5,6]. The literature has described cases of malignant PASAT patients without hirsutism. These cases could be explained by abrupt tumoral appearance, without leaving time for androgens to act on hair receptors and manifest this sign [3].

### Diagnosis

A biochemical confirmation, using DHEAS and increased total testosterone (12-fold above the upper limit of normal range orients to malignancy) [3] will confirm the clinical suspicion. Some authors suggest that dynamic tests should be performed, such as dexamethasone androgen suppression test for establishing a differential diagnosis between an adrenal tumor and other causes of hyperandrogenism. A decrease in post-dose androgens of at least 40% allows the identification of non-tumor pathology with a sensitivity of 100% and a specificity of 88%, given that adrenal tumors secrete androgens autonomously without ACTH regulation [7].

Diagnosing PASATs in males represents a challenge for the clinician since they are only evident when the peripheral androgen-to-estrogen conversion is present [8].

Imaging diagnostic tools include abdominal CT as the initial approach, followed by MRI or <sup>18</sup>F-FDG PET-CT. This last technique reveals its usefulness in evaluating intratumoral metabolic rate [9,10]. In our case, due to the CT characteristics and the equipment's availability, an <sup>18</sup>F-FDG PET-CT was requested, and it revealed low

intratumoral metabolism.

PASATs are almost always large-sized, which is not surprising since the adrenal glands secrete few androgens compared to virilizing ovarian tumors, which are often small and may even be hidden [11]. The maximum diameter of the adrenal mass typically predicts malignancy; however, in PASATs, the size does not always correlate with malignancy probability. A series of 9 cases presented by Tong et al. described two adenomas exceeding 9 cm [1]. Unlike adrenal carcinomas, which generally have a larger size, the literature usually reports that most adrenal adenomas are less than 4 cm to 6 cm in diameter, confusing the diagnosis [12].

In addition to the size, the classic imaging features that guide us to tumor benignity, such as the lipid-rich nature (Hounsfield units <10) or a contrast wash-out >60% of the 10-min protocol, also generate confusion, since the PASATs do not always comply with them [13].

### Treatment

The surgical approach is recommended in all functioning adrenal tumors. Some authors recommend the open approach in tumors larger than 10 cm with or without suspected malignancy. Otherwise, the laparoscopic approach may be considered. Complete surgical removal is the key to a good prognosis [3,14]. Finally, the definitive diagnosis will be established through the pathologic report of the surgical specimen, using the Weiss criteria (Table 1) [15].

Regarding the follow-up, Moreno et al. did not show an increase in androgen levels or post-surgical tumor relapse in their series of 11 benign PASAT patients, who were followed for an average of 17 years [3].

In summary, our case presents a 47-year-old female, without previous illness, who had a progressive clinical course of hyperandrogenism and virilization and was diagnosed as a PASAT with no evidence of malignancy in the right adrenal gland, and an adenoma in the left adrenal gland. She had an excellent post-surgical evolution and no clinical, biochemical, or structural recurrence than the different case series findings. Provided a contralateral adenoma, a clinical follow-up is proposed, requesting a new image in case of recurrence of symptoms.

### Conclusion

PASATs are rare tumors that predominate in the female sex. The diagnosis is achieved by clinical suspicion with signs of hyperandrogenism and virilization, elevated serum androgen levels, and imaging evidence of adrenal tissue lesion. Nevertheless, these elements are not enough to make an accurate diagnosis, being the pathological report of foremost importance for the definitive diagnosis. The 18F-FDG PET-CT is a new diagnostic tool to take into account to assess tumor characteristics. Surgical treatment is the gold standard, and the approach will depend on the size and tumor characteristics. The pathological report will determine the medium and long-term prognosis.

### Recommendations

PASATs must be considered when a differential diagnosis for female patients with hyperandrogenism and virilization is made. It should be emphasized that a significant increase in serum total testosterone is not always associated with ovarian pathology. After surgical treatment and in search of new manifestations of hyperandrogenism, it is suggested to carry out clinical and laboratory follow-up every six months in the first year, and further on, a clinical follow-up.

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