# Androgen secreting giant adrenocortical carcinoma with no metastases: A case report and review of the literature

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# Abstract

Functional adrenocortical carcinoma (ACC) is a very rare disease with a poor prognosis. Over half (60%) of ACCs bigger than 6 cm synthesize hormones; hormone-secreting ACCs generally include virilization, feminization or Cushing syndrome. Besides, 82% of ACCs are metastatic at the time of diagnosis. While a 48-year-old female patient was examined for abdominal pain and flushing, we detected a non-metastasizing mass (23 × 18 × 16 cm) in the adrenal lodge. The mass was extracted en bloc during open exploration and its histopathology was reported as ACC. We review the literature and report the largest androgen-producing, clinically silent ACC mass cited in the literature so far.

# Introduction

Adrenocortical carcinoma (ACC) is a very rare malignant tumour (0.02% of all cancer types); its incidence in adults is 1/1.7 million.<sup>1,2</sup> ACC demonstrates a bimodal distribution and its incidence peaks before 5 years old and between 40 and 50 years old.3 Most of ACCs are sporadic, but its congenital and familial types can be encountered.<sup>4,5</sup> It is seen 1.5 times more frequently in women. ACCs are larger than benign adrenal masses and measure about 10 to 12 cm. ACCs accounts for 2% of adrenal tumours that are 4 cm or less, 6% of tumors that are 4.1 to 6 cm, and 25% of tumours that are greater than 6 cm.<sup>6</sup> On the other hand, over 90% of ACCs are bigger than 6 cm. They weigh 0.1 to 1.0 kg. Adrenal masses divide into 2 groups: hormone-secreting tumours and non-secreting tumours. About 60% of ACCs synthesize hormones. Hormone-secreting ACC presents itself with manifestations of virilization, feminization or Cushing syndrome; hormone-non-secreting ACCs are usually diagnosed incidentally.<sup>7,8</sup> Even if the tumour is extirpated completely, recurrence or distant metastases are encountered in

many patients.<sup>9</sup> For staging, the ENSAT (European Network for the Study of Adrenal Tumours) classification is used.<sup>4</sup> Five-year survival rates in stage I, II and III disease are 84%, 63% and 53%, respectively; the stage IV 1-year survival rate is nearly 15%.<sup>10,11</sup> In early stage ACC, age <40, absence of lymph node involvement and distant metastases are positive prognostic factors, while tumours larger than 12 cm diameter carry adverse prognostic factors.<sup>12</sup>

Negative surgical margins increase survival rates independent from other factors. Though spontaneous regression has been reported, 82% of ACCs are metastatic at diagnosis. It metastasizes most frequently to lungs (71%), lymph nodes (68%), liver (42%), bones (20%), and inferior vena cava (20%).<sup>13</sup> The only curative treatment is surgical resection. Survival rates of inoperable patients are very low. In the systemic treatment of ACC, despite its toxicity and lower response rates, an adrenolytic agent mitotane can be used.<sup>14,15</sup> We report a case of the largest but clinically silent, androgen-producing, non-metastasizing ACC mass.

# **Case report**

During ultrasonographic examination of a 48-year-old female patient with abdominal pain and flushing, we detected a hypoechoic solid adrenal mass. Her medical history did not reveal any comorbid disease or regular use of any medication. On physical examination, a mass was palpated at the left hypochondriac region and she had minimally frontal balding. Her average blood pressure was 130/80 mmHg on 24-hour ambulatory blood pressure monitoring. Her serum aldosterone, potassium, renin, 24-hour urine metanephrine levels, and dexamethasone suppression test results were within normal limits. Only levels of serum total testosterone and dehydroepiandrosterone sulfate (DHEA-S) were measured (1.28 ng/mL and >1500 µg/dL, respectively) (Table 1). A magnetic resonance image (MRI) demonstrated a heterogeneously enhancing mass lesion in the left adrenal lodge with cystic-necrotic components measuring 208 mm × 138 mm



Fig. 1. Contrast-enhanced magnetic resonance image: Coronal plane.



*Fig. 2.* Contrast-enhanced magnetic resonance image: Transverse plane.

and deplacing the pancreas and splenic vein superiorly and left kidney inferiorly (Fig. 1, Fig. 2). Positron emission tomography-computed tomography (PET/CT) was performed for metastatic workup and pathologic 18-fluorodeoxyglucose (FDG) uptake was not encountered. The patient was referred to the department of endocrinology; preoperative nifedipine at daily oral doses of 60 mg were initiated. Through a modified Chevron incision, we explored the surgical field, reached the mass and extirpated it en bloc (Fig. 3). Her perioperative blood pressure values remained stable. The histopathology revealed an encapsulated mass with smooth contours weighing 1300 gr, with dimensions of  $23 \times 18 \times 16$  cm, which was identified as adrenocortical carcinoma demonstrating increased mitotic activity (Fig. 4). Immunohistochemically, it was stained positively with vimentin, synaptophysin and cytokeratin (Fig. 5). Its mitotic and Ki-67 proliferation indices were reported 56/50 and 11% to 13%, respectively. During her follow-up visits, DHEA-S and total testosterone levels

Table 1. Pre- and postoperative hormone levels of patients			
	Pre- operative	Post- operative	Range
DHEA-SO4 (ug/dL)	>1500	144.6	56–283
Cortisol (ug/dL)	9.3	9.1	3.7–19.4
Metanephrine (ug/24h urine)	61.37		52– 341
Normetanephrine			
(ug/24h urine)	323. 32		88–444
VMA (mg/24h urine)	3.8		3–9
Aldosterone (ng/dL)	20.9		7–30
Renin (ng/mL/hour)	4.24		(2.9–10.8)
Total testosterone			
(ng/mL)	1.28	0.45	0.13–1.08
Prolactin (ng/dL)	19.19		5.18-26.53
Estradiol (pg/mL)	97		1–147
VMA: Vanilly Imandalia asidy DHEA SO() deby draggion dragt and reactor and sulfate			

VMA: VanillyImandelic acid; DHEA-SO4: dehydroepiandrosterone sulfate.

observably regressed to their normal reference ranges. The patient was referred to medical oncology during the postoperative period. The medical oncologist started mitotane treatment and treatment is ongoing.

### Discussion

Sex hormone-secreting tumours are more likely malignant. Feminization is more closely associated with malignancy rather than virilization.<sup>16</sup> Feminizing ACCs are rare and constitute only 1% to 2% of all adrenocortical malignancies.<sup>7</sup> High levels of DHEA-S are another marker for ACC, whereas decreased serum DHEA-S concentrations suggest benign adenoma.<sup>17</sup> Androgen-secreting tumours can produce hirsutism and virilization in 90% to 100% of patients and amenorrhea in 40% to 60% of patients.<sup>18</sup> Our patient had none of these symptoms, though her DHEA-S level was very high (>1500 ug/dL).

ACCs are generally detected incidentally; the CT and MRI are other diagnostic radiological modalities. F-fluorodeoxyglucose (FDG)-PET/CT is still considered complementary and not recommended for ACC workup.<sup>19</sup> Although lesion detection is similar between PET/CT and CT, PET/CT may be preferred to assess chemotherapeutic response.<sup>20</sup> When we reviewed the literature, we observed that only 25% to 30% of patients were in stage 1-2 (organconfined disease), while 70% were in stage 3-4 (invasion beyond adrenal gland).<sup>19,21</sup> Our patient was in stage 2. Treatment alternatives consist of surgical treatment and/ or adjuvant chemotherapy and/or adjuvant radiotherapy. The most important step of curative treatment constitutes complete resection of primary or recurrent tumour. Even after larger surgical resection, many patients experience recurrence and distant metastases.<sup>9</sup> Even among patients who had undergone radical surgery, local recurrence and metastasis were seen in nearly 80% of cases.<sup>21</sup> Many studies have demonstrated favourable effects of tumour resection



*Fig. 3.* Macroscopic view of en bloc specimen: an encapsulated mass with smooth contours weighing 1300 gr, with dimensions of  $23 \times 18 \times 16$  cm.

on survival rates. Moreover, resection of recurrent tumours ensures palliation of hormonal symptoms in patients with functional ACC.<sup>22</sup>

Higher recurrence rates of ACCs have led the researchers to search for adjuvant treatment modalities. As adjuvant treatments, cytotoxic drugs, molecular targeted therapies, radiotherapy and other locally ablative modalities have been tried, with no promising outcomes.<sup>23</sup> Mitotane is a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane used for this purpose. Terzolo and colleagues<sup>24</sup> conducted a retrospective multicentered study in Italy and Germany and associated higher recurrence-free and overall survival rates to adjuvant mitotane treatment in ACC patients whose tumours were completely resected without residual tumour as demonstrated by histopathological and radiological examinations.

In many studies, advanced stage tumour and incomplete surgical resection are the main factors associated with poor prognosis. Also, high grade, advanced age, hormone secretion, gender and large tumour size are correlated with poor prognosis.<sup>25</sup> Bilimoria and colleagues<sup>26</sup> reviewed 3928 patients. They found that the worse prognostic factors were: advanced age (>55), positive surgical margins, lymph node positivity, distant metastasis, and resection of adjacent organs. They also evaluated tumours according to size in two groups (smaller than 10 cm and larger than 10 cm in diameter); these sizes were not correlated with a poor prognosis.

Though precise histological criteria to define malignant adrenal masses are lacking, the histopathological factor most related to prognosis described by Weiss in 1984 is frequently used. The presence of 3 or more criteria from 9 histological criteria has been evaluated in favour of malignancy.<sup>27</sup> In our patient, 4 of the 9 criteria were present, namely capsular invasion, cellular atypia, mitotic index >5/50 (56/50), and microscopic necrosis.



*Fig. 4.* Hematoxylin and eosin stain of the adrenal gland. Arrows: Adrenocortical carcinoma. Inferior: Residual rim of normal adrenal gland (100×).

Immunohistochemical assessment of the nuclear antigen Ki-67 can be useful in the differential diagnosis between adrenocortical adenoma and carcinoma. Studies have demonstrated that a higher Ki-67 proliferation index is associated with poor prognosis and an inverse and significant correlation exists between this index and overall survival rate.<sup>23</sup> In our patient, the Ki-67 proliferation index was 11% to 13%.

#### Conclusion

Sex hormone-secreting ACCs are very rarely seen in urology practice. We reviewed the literature and reported a case with the largest-sized non-metastasizing, androgen-producing but clinically silent ACC mass.

Competing interests: The authors all declare no competing financial or personal interests.



Fig. 5. Immunohistochemical stain: synaptophysin (100×).

#### Androgen secreting giant adrenocortical carcinoma

This paper has been peer-reviewed.

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