Case Report

Pitfall in the Diagnosis of an Aggressive Adrenal Mass with Prominent Hirsutism: A Case Report

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Abstract

Here, we present the case of a 74-year-old woman with clinically prominent hirsutism and a large adrenal mass where the clinical diagnosis was inconsistent with the histological appearance. Her hormonal evaluation showed normal androgens with slightly inadequate cortisol suppression upon dexamethasone test but normal 24-h urinary free cortisol. Abdominal computed tomography (CT) imaging showed a large inhomogeneous mass of the left adrenal and the FDG PET/CT scan revealed hypermetabolic foci in the right upper lobe of the lung, in hilum lymph nodes, and in the soft tissue in proximity to the right femoral neck. The cytological examination of a biopsy from the pulmonary lesion showed a highly malignant neoplasm of unknown origin, and left adrenalectomy, nephrectomy, and splenectomy were performed. The pathologists reported infiltration of the adrenal by an undifferentiated carcinoma of unknown origin. Due to the clinical suspicion of adrenocortical carcinoma (ACC), a mitotane therapy along with hydrocortisone substitution was directly initiated, and the patient also received 6 cycles of chemotherapy. However, the patient's condition deteriorated quickly, and she died. Upon availability of steroidogenic factor-1 staining, the positivity of the resected tumor could be documented postmortem, confirming the diagnosis of an ACC. Taken together, this case underlines the difficulties in the differential diagnosis of aggressive adrenal masses.

Keywords: Adrenocortical carcinoma, adrenalectomy, hirsutism

Adrenocortical carcinoma (ACC) is a rare condition, with an incidence of 1–2 cases per million[1] and poor prognosis, with a 5-year survival of 60% for tumors confined to the adrenal gland, 35%–50% for locally advanced disease, and approximately 15% for metastatic disease.[2–4] ACC may be asymptomatic and diagnosed incidentally or present with unspecific symptoms due to local tumor growth or appear with a hormonal syndrome, most commonly with

Cushing's syndrome or mixed Cushing's syndrome and virilization, whereas feminization and Conn's syndrome occur rather rarely.[5]

Case Report

We herein report an unusual case of a 74-year-old woman (study approved by the Scientific Committee of "Laiko" University Hospital, audit number: 1108/22-01-2021) who presented to our outpatient clinic with pronounced facial hirsutism of recent onset and a large adrenal mass. The case presented a diagnostic challenge as her clinical appearance was inconsistent with the histological diagnosis.

Besides a fracture, due to an accident 5 years ago, the medical record of the patient was blank. She had menarche at the age of 13 years, regular menstruations every 28–30 days, with a duration of 3 days, reported dysmenorrhea, and a first-trimester abortion at the age of 38. The patient had no other pregnancies in her obstetric history. She had a smoking history of 5 pack/year. Upon clinical examination, she presented whole body lanugo, developed within the past 2 months, which was much more pronounced in the face area. Furthermore, muscle weakness of the lower extremities was observed, and a large goiter was palpable. At presentation, the patient weighed 52 kg (BMI 23.4 kg/m^2), with a sitting blood pressure of 145/92 mmHg (pulse 85 min^{-1}) and female adipose tissue distribution. At the time, she empirically received 40 mg pantoprazole and 10 mg domperidone daily, due to undiagnosed gastric symptoms.

Upon admission, the patient had normal serum sodium (142 mmol/L), slight hypokalemia (3.3 mmol/L), and normoglycemia (87 mg/dL). The biochemical tests did not identify any particular abnormalities. The hormonal evaluation showed low or low-normal androgen values [dehydroepiandrosterone (DHEA), DHEA sulfate, Δ4-androstenedione, 17-OH progesterone, and free testosterone index], with an only slightly insufficient cortisol suppression upon overnight dexamethasone test (2.17 μg/dL), and a normal adrenocorticotropic hormone (ACTH) value. Luteinizing (LH) and follicle-stimulating hormone (FSH) were within the normal range for postmenopausal women. The aldosterone-to-renin ratio (ARR) was also slightly increased. Thyroid-stimulating hormone (TSH), fT4, and calcitonin were within the normal range (Table 1). Additionally, laboratory findings showed increased levels of carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), with slightly increased levels of chromogranin A (CgA). In parallel, the bone mineral density of the left femoral neck was compatible with severe osteoporosis with a T-score of -3.47. Thyroid ultrasonography confirmed the presence of a large goiter with a 5 × 5 cm large nodule in the left lobe (Fig. 1). A fine needle aspiration (FNA) biopsy of the thyroid nodule was performed, and the cytology revealed a lesion compatible with benign disease (The Bethesda System for Reporting Thyroid Cytopathology II).

Abdominal computed tomography (CT) imaging showed a 7.8-cm large inhomogeneous mass of the left adrenal gland. After 1 month, in the magnetic resonance imaging,

Table 1. Laboratory workup

Parameter	Value	Normal	Parameter	Value	Normal
Cortisol (μg/dL)	14.6	5–23	Prolactin (ng/mL)	10	4.8–23.3
ACTH (pg/mL)	11.3	5–60	FSH (IU/L)	45.1	25–134
Cortisol after 1 mg dexamethasone (μg/dL)	2.17	<1.8	LH (IU/L)	27.7	7.7–85
PRA (ng/mL/h)	0.12	0.6–4.3	E2 (pg/mL)	<9	<50
Aldosterone (ng/dL)	5.92	4–31	TSH (μU/mL)	0.99	0.3–4.2
ARR	49	<30	fT4 (ng/dL)	1.14	0.7–2
U metanephrines (μg/24 h)	391	100–800	PTH (pg/mL)	113	15–65
U normetanephrines (μg/24 h)	326	88–444	Calcitonin (pg/mL)	0.8	<8
Δ4-androstenedione (ng/mL)	0.4	0.3–3.0	CEA (ng/mL)	81.7	<6.5
Total testosterone (ng/dL)	23	5–52	β-HCG (U/L)	5	<5
SHBG (nmol/L)	196	20–130	CgA (nmol/L)	5	<4
DHEA sulfate (ng/mL)	<15	35–430	NSE (μg/L)	34.7	<16
DHEA (ng/mL)	0.8	1–10.5	a-FP (ng/mL)	4.9	<15
17-OH progesterone (ng/mL)	0.38	0.2–1.0	CA 19-9 (U/mL)	<7.4	<39
Progesterone (ng/mL)	<0.17	<0.2	CA 125 (U/mL)	23.4	<35

ACTH: Adrenocorticotropic hormone; PRA: Plasma renin activity; ARR: Aldosterone-to-renin ratio; SHBG: Sex hormone binding globulin; DHEA: Dehydroepiandrosterone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; TSH: Thyroid stimulating hormone; PTH: Parathormone; CEA: Carcinoembryonic antigen; β-HCG: β-human chorionic gonadotrophin; CgA: Chromogranin A; NSE: Neuron-specific enolase; a-FP: a-fetoprotein; CA: Cancer antigen.
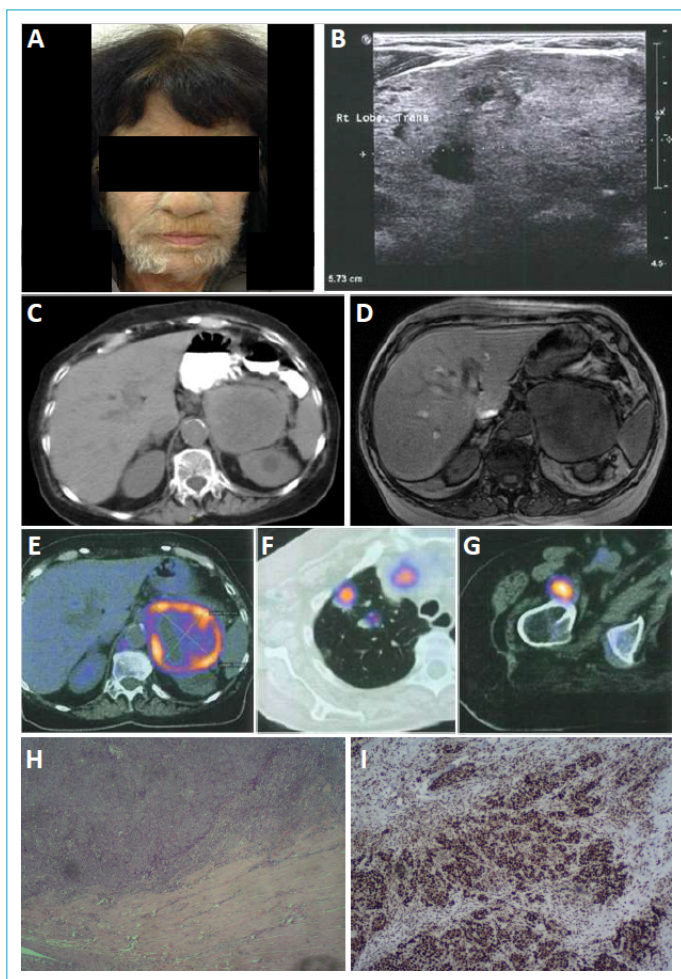
Figure 1. (a) Virilizing phenotype of the patient; **(b)** ultrasound of the thyroid gland; **(c)** abdominal CT scan; **(d)** retroperitoneal magnetic resonance imaging scan. FDG PET imaging, with hypermetabolic foci **(e)** in the area of the adrenal gland, **(f)** in the right upper lobe of the lung, and **(g)** in the soft tissue in proximity to the right femoral neck; **(h)** hematoxylin/eosin staining of the tumor (50×); (i) SF-1 immuno-histochemical staining (50×).

the adrenal mass measured 8.5 cm, with central necrosis. After 1 week, the FDG PET/CT confirmed the presence of the lesion of the left adrenal gland, measuring 8.9 cm, with a SUVmax of 13.5. Hypermetabolic foci with increased FDG uptake were also seen in the right upper lobe of the lung, in several lymph nodes of the right pulmonary hilum, and in the soft tissue close to the right femoral neck (Fig. 1). To identify the tumor origin, a CT-guided biopsy of the largest pulmonary lesion was performed. The cytological examination showed small-to-medium-sized malignant cells of unknown origin (negative for TFT, CD56, and P63).

Due to the progression rate, left adrenalectomy, nephrectomy, and splenectomy were performed. The pathologists reported extensive infiltration of the adrenal gland by an undifferentiated carcinoma of unknown origin with pro-

nounced polymorphism, nuclear atypia, and high mitotic rate (52/10 HPF, ki-67: 70%, positive for CKAE1/AE3, CK8, CD10, EMA, NSE, CgA, synaptophysin, pCEA, and CDX2; weakly positive for vimentin, CK20, and mCEA; negative for CK7, CK5/6, P63, thrombomodulin, TTF1, TG, GCDFP 15, RCC, S100, Mart1, CD117, calretinin, PLAP, CD30, CD5, inhibin, and HepPar1).

A mitotane therapy (with dose titration from 500 mg up to 2 g daily, and subsequently according to the mitotane plasma levels, to remain within the therapeutic window) along with hydrocortisone substitution (25 mg daily) were directly initiated and the patient also received 6 cycles of chemotherapy (cisplatin and etoposide). Because of rapid disease progression, a revision of the pathology was requested. This confirmed infiltration of the adrenal gland by a solid adenocarcinoma with extensive necrosis [ki-67 > 60%, positive for 8.18 EMA, CEA, BerEP4, EMA, and in parts CDX2; weakly positive (<5%) for CgA and synaptophysin; negative for PDX1, TTF1, inhibin, melan-A, and NF]. A steroidogenic factor-1 (SF-1) immunohistochemical staining was not available at that time. However, before the initiation of further treatment, the patient's condition deteriorated quickly. Due to an episode of loss of consciousness, a brain CT scan was performed and brain metastases were identified. Before the initiation of local radiotherapy, the patient died. Later, upon the availability of SF-1 staining, this was performed on the obtained slides from the resected adrenal tumor, which showed very pronounced expression, supporting the suspicion of an ACC.

Discussion

We present here the case of a patient with a clinically evident hormonal syndrome and a large adrenal mass along with the extensive metastatic disease. The differential diagnosis, besides an ACC, included a primary adrenal lymphoma, a metastasis from lung carcinoma, renal cell carcinoma, or carcinoma of unknown primary. From the laboratory workup, a possibly autonomous cortisol secretion was documented, suggestive of an ACC. Still, the low normal or even suppressed androgens could not explain the prominent hirsutism of the patient. We hypothesize that this clinical symptom originated from nonquantified steroid metabolites secreted by the tumor. Still, the ACTH and LH levels measured in this patient did not fully correspond to the expected inhibition of these two peptides. Cortisol suppression upon 1 mg dexamethasone test just exceeded the cutoff of 1.8 μg/dL, applied in our clinic with strict criteria. However, the usage of different cutoffs (e.g., 5 μg/dL) is also used in clinical practice, to increase the specificity of the test. Thus, a clear cortisol excess could not be documented in this patient at the time of diagnosis. It can,

though, be speculated that cellular dedifferentiation in this rapidly progressive adrenal tumor altered the hormonal profile, while the clinical appearance of the patient could not be affected so promptly.

The unilateral adrenal localization of the tumor and its large size were also suggestive of an ACC. However, the spindle-shaped intrapulmonary lesion with concurrent hilum lymph nodes raised the suspicion of a pulmonary primary. Furthermore, no clear conclusions about the origin of the tumor could be drawn from the initial pathological examination of both the pulmonary and the adrenal lesion. The presence of EMA expression, often observed in renal cell carcinomas but rarely documented in ACCs,[6] and the positivity for gastrointestinal and pulmonary tumor markers, together with the absence of typical ACC markers, such as melan A and inhibin, questioned the diagnosis of an ACC.[7] Still, the positivity for vimentin, NSE, and in parts for synaptophysin and CgA were suggestive of the adrenocortical origin of the tumor. Although SF-1 can occasionally be positive in renal cell carcinomas,[6] the combination of the clinical picture with the positive SF-1 staining was the crucial step to substantiate the diagnosis of ACC. This, however, was only possible postmortem, upon audit, in the present case, whereas respective SF-1 staining of the lung biopsy, to confirm the adrenocortical origin of the pulmonary lesions was not feasible, as no cell block was produced from the FNA, and the patient's family had denied an autopsy.

Taken together, this case underlines the difficulties in the differential diagnosis of rapidly progressive adrenal masses and the diagnostic challenges when the clinical appearance is inconsistent with the histological analysis.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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