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Case Report

Feminizing Adrenocortical Tumor with Multiple Recurrences: A Case Report

Joseph M. Rich[a] Vinay Duddalwar[b, c, d] Phillip M. Cheng[b] Manju Aron[e] Siamak Daneshmand[d]

[a]MD/PhD Program, USC-Caltech MD/PhD Program, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; [b]Department of Radiology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; [c]USC Radiomics Laboratory, Keck School of Medicine, Department of Radiology, University of Southern California, Los Angeles, CA, USA; [d]Department of Urology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA; [e]Department of Pathology, Keck School of Medicine of USC, Los Angeles, CA, USA

Keywords
Estrogen-secreting tumor · Feminizing adrenocortical tumor · Gynecomastia

Abstract
Feminizing adrenocortical tumors (FATs) are exceptionally rare primary adrenal neoplasms that cause high estrogen and low testosterone levels. They are most common in adult males, typically presenting with gynecomastia, hypogonadism, and weight loss. They are almost always malignant, with a poor prognosis and a high recurrence rate. We report a case of a 35-year-old man with an adrenal FAT with high estrogen (181 pg/mL) and low testosterone (37 ng/dL) who presented with gynecomastia, erectile dysfunction, subclinical Cushing syndrome, and pain localizing to different regions of the torso. There was no evidence of metastatic disease initially as seen by visualization of a well-marginated mass on computed tomography scan. Surgical resection of the FAT was performed, and the mass was confirmed to be a low-grade tumor. Clinical symptoms were resolved after surgery. Despite complete resection with negative margins, the patient subsequently had two separate local metastatic recurrences within a few years, treated with a combination of further surgery and medical intervention. This case highlights the unique features of an exceedingly rare adrenal tumor and stresses the importance of early detection and vigilant surveillance following resection due to high recurrence rates.

Correspondence to:
Joseph M. Rich, jmrich@usc.edu

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Introduction

Adrenocortical tumors are often found incidentally with cross-sectional imaging, with the most common being an adrenal adenoma. Primary malignant tumors include adrenocortical carcinoma and pheochromocytoma. The adrenal cortex is also a common site for metastatic disease [1]. Primary carcinomas of the adrenal gland are very rare, with an incidence in the USA of around 200 people per year for adrenocortical carcinomas and 500–1,600 people per year for pheochromocytoma and paraganglioma [1]. Adrenal adenomas or adrenocortical carcinomas are usually nonfunctioning, but they may secrete corticosteroids and/or sex steroids. Depending on the hormone secreted, patients may present with Cushing syndrome (commonest, produced by 5–20% of adrenal incidentalomas) or Conn's syndrome [2].

The feminizing adrenocortical tumor (FAT) is a functional primary adrenocortical tumor that solely secretes estrogens (estradiol and estrone). FATs can either manifest as benign estrogen-secreting adrenal adenomas or as malignant estrogen-secreting adrenocortical carcinomas, with the malignant variant being much more common. As a result of high estrogen, testosterone levels are usually suppressed. FATs are exceedingly rare, accounting for less than 2% of all adrenal neoplasms [3]. There were only 50 reported cases in the literature between 1970 and 2015 [4], and only a small additional number since that time. These are most commonly seen in adult males. Presenting signs/symptoms in adult males commonly include gynecomastia, hypogonadism, and weight fluctuation (either loss or gain, with loss being more common); in adult females, there is irregular or postmenopausal bleeding; in pediatric males, there is contrasexual precocious pseudopuberty; and in pediatric females, there is isosexual precocious puberty [5]. In pure FATs, there is usually a lack of signs or symptoms of Cushing syndrome, hypertension, and virilization/hirsutism, differentiating FATs from mixed functional adrenocortical tumors. Diagnosis is made by a combination of clinical factors (including gynecomastia, change in libido, and erectile dysfunction in adult males), serum laboratory values (including elevated estrogen), radiologic imaging findings (i.e., a visualized adrenal mass), and immunohistochemistry (IHC) imaging findings (i.e., α-aromatase positivity) [4]. Radiologically and histologically, FATs appear broadly similar to other primary adrenal masses with the exception of α-aromatase positivity for FATs [4]. Distinguishing malignant from benign FATs is challenging, but can be assisted with radiographic findings (i.e., irregular borders, heterogeneity, invasion, etc.), histology (i.e., a high Weiss score), or recurrence/metastases [4].

While adrenal adenomas generally have an excellent prognosis, adrenocortical carcinomas carry a poor prognosis, with the FAT subtype of adrenocortical carcinomas having the worst prognosis among these carcinomas [6]. No specific causal mutations are linked to FATs, but some suspected implicated genetic alterations involve IGF2, the Wnt/β-catenin pathway, and TP53.1 mutations [7]. Advanced stage upon diagnosis is one of the strongest indicators of poor prognosis [8].

The number of published case reports of FATs is low due to the rarity of the disease. Here, we present a case of a 35-year-old man with significant gynecomastia, reduced libido and erectile function, subclinical Cushing syndrome (SCS) with progressive weight gain, and continual recurrence despite surgery. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533835). Case reports of this condition are important to increase awareness of the disease and to emphasize early diagnosis and treatment.

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Case Report

A 35-year-old man presented with new acute right upper quadrant (RUQ) abdominal pain in December 2019. He also presented with a self-reported 8-month history of significant gynecomastia, 6-month history of reduced libido and morning erections, and progressive weight gain and obesity (body mass index of 36). He denied galactorrhea or decrease in testicular size. He had no history of hypertension, flushing, sweating, palpitations, headache, or diabetes mellitus. He was not taking any medications. There was no family history of endocrine disorders or genitourinary malignancies. Physical exam confirmed RUQ pain and gynecomastia and was negative otherwise.

Laboratory values showed low follicle-stimulating hormone (<0.1 mIU/mL), low luteinizing hormone (<0.1 mIU/mL), low testosterone (37 ng/dL), high estradiol (181 pg/mL), normal cortisol (8.0–14.5 μg/dL), low adrenocorticotropic hormone (ACTH) (1 pg/mL), and normal norepinephrine levels (524 pg/mL). Low-dose dexamethasone test showed unsuppressed cortisol.

A computed tomography (CT) scan of the abdomen revealed a large heterogeneous right adrenal mass (18 × 8.5 × 14.5 cm) of predominantly soft tissue density. It was highly vascularized, with a large number of collaterals and focal areas of high enhancement (Fig. 1a–b). It appeared well-defined and was not noted to invade or infiltrate into adjacent viscera and tissues. No metastases were noted. The diagnosis of an adrenal tumor was made, but differentiation between a benign versus malignant tumor could not be made with CT alone. Magnetic resonance imaging confirmed a solid heterogeneous enhancing mass which was well marginated, concerning for adrenocortical carcinoma (Fig. 1c).

Given the combination of a malignant adrenal mass, high estrogen, and lack of other hormonal symptomatology (i.e., Cushing syndrome, hypertension, and virilization), it was determined that the patient had an FAT. Pheochromocytoma was considered due to location but was ruled out due to normal serum metanephrines/normetanephrines and pathological findings described below.

Surgical resection was performed within days of diagnosis. At surgery, the tumor was confined to the adrenal gland without apparent invasion of adjacent structures. The resection margin was negative.

On gross examination, the tumor was 18 cm in greatest dimension, predominantly yellow in color, and circumscribed with prominent areas of hemorrhage and necrosis (Fig. 2a). On microscopic examination, the tumor was predominantly eosinophilic (>50% of tumor cells), mitotically active (10 mitotic figures per 50 high-power fields) with extensive tumor necrosis (>80%) (Fig. 2b, c). Lymphovascular and capsular invasion were not identified. The MIB-1 index was 10–20%. The modified Weiss score of the tumor was 5, indicating malignancy based on histopathological findings. The tumor cells were positive for inhibin and calretinin, further supporting the adrenal cortical origin of the tumor. The nonneoplastic adrenal gland was atrophic.

Two months post-op, he sustained normalization of hormone parameters (Table 1), gynecomastia decreased to near baseline, and libido/erections returned to normal. There was still excess adiposity, with some mild persistent swelling around the areolas. No weakness, fatigue, or other signs/symptoms of adrenal insufficiency were reported. Cosyntropin stimulation test revealed some cortisol suppression, but due to lack of clinical presentation and the ability to use cortisol as a tumor biomarker, the patient was not started on hydrocortisone therapy.

18 months post-op, in May 2021, another chest X-ray and contrast abdominal and pelvic CT surveillance was performed, revealing a new 1 cm nodule in the right adrenalectomy bed. A previous 0.9 cm mass (diagnosed 1 year prior) central from the inferior right hepatic lobe posterior to right kidney grew to 1.4 cm, concerning for local recurrence (Fig. 3). Testosterone levels remained within normal range but had dropped substantially since last recorded; estrogen levels had substantially risen since last recorded (Table 1).

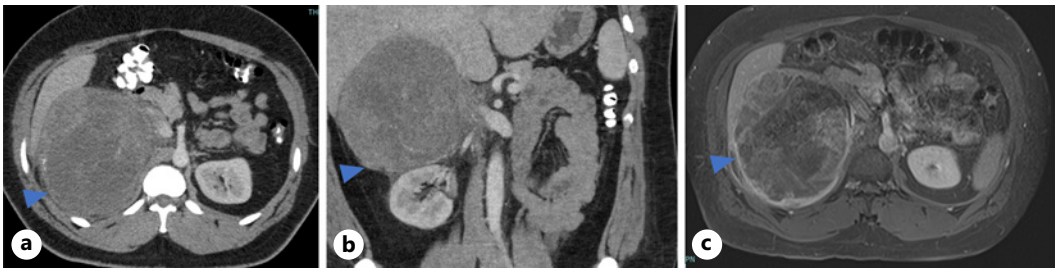

Fig. 1. Axial (**a**) and coronal (**b**) contrast-enhanced CT scans upon diagnosis. There is a large, heterogeneous, predominantly soft tissue mass replacing the right adrenal and displacing the kidney and liver. The mass (blue arrows) is well-marginated with no obvious infiltration into surrounding tissues and no intra-venous extension. A few intratumoral streak-like linear densities are from neovascularity. Axial post-contrast T1-weighted MR image (**c**) depicts the heterogeneous nature of the well-marginated right adrenal tumor (blue arrow).

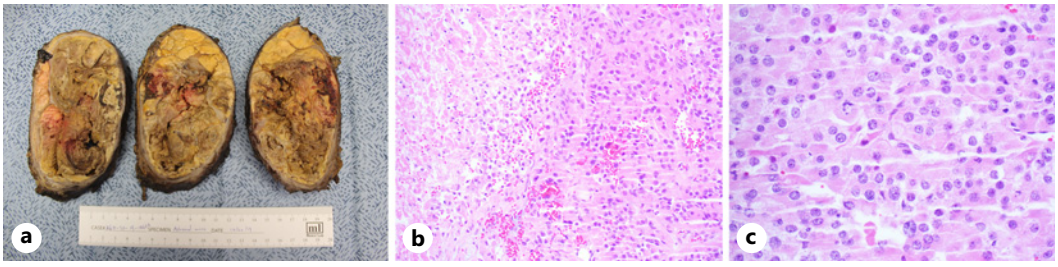

Fig. 2. Pathological findings of the primary tumor specimen. **a** Gross tumor demonstrating predominantly yellow color with areas of hemorrhage and necrosis. **b–c** Light microscopy of the tumor showing adrenal cortical carcinoma with necrosis ×20 (**b**) and mitosis (**c**).

The patient presented with worsening gynecomastia, erectile dysfunction, and steatosis in September 2021. Previous nodules had grown and multiple metastatic hepatic and retroperitoneal nodules had appeared, which were surgically resected. Potentially, metastatic hepatic and perihepatic nodules up to 2 cm appeared in December 2022 and enlarged by April 2023, indicating locoregional recurrence of the disease after nearly three and a half years since initial diagnosis of the primary tumor. Plans include chemotherapy with mitotane or etoposide/doxorubicin/cisplatin given the slow progression and low grade of the disease, with surgery not indicated due to recurrent metastatic disease.

Discussion

Atypical characteristics of this case include pain (RUQ abdominal, back, flank, and chest), most likely attributable to the size of the mass, weight gain, and severe obesity, unsuppressed cortisol despite normal laboratory values, steatosis, and development of a ventral hernia following surgery. Although originally attributed to musculoskeletal causes by the clinicians on this case, flank pain has been associated with FATs in the past [9]. Contributing factors to gynecomastia include hyperestrogenism, androgen deficiency, and hepatic failure [6]. The steatosis in our patient could have compounded in causing the persistent gynecomastia.

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Table 1. Laboratory values and clinical syndromes pre-op, post-op, and on surveillance

Compound or clinical symptom	Pre-op (12/2019)	Post-op (1/2020)	Surveillance (5/2021)	Normal
Estradiol, pg/mL	181 (H)	9–19.0	88.9	10–50
Testosterone, ng/dL	37 (L)	436 ng/dL	305	300–1,000
FSH, mIU/mL	<0.1 (L)	14.9 (H)		1.5–12.4
LH, IU/mL	<0.1 (L)	19.5 (H)		1.8–8.6
Albumin, g/dL	2.8 (L)		4.2	3.4–5.4
17-OH Prog, ng/dL	71.44			<200
Cortisol, μg/dL	8.0–14.5			5–25
ACTH, pg/mL	1.0 (L)			5–50
Aldosterone, ng/dL	<3.0			3–25
Metanephrine, nmol/L	<0.3			<0.9
Renin activity, ng/mL/h	0.10 (L)			0.6–4.3
Urine cortisol free 24 h, μg/24 h	111.1 (H)			10–100
Urine cortisol free, zzμg/g_crt	49.64			10–100
Cushing's syndrome	No	No	No	
Gynecomastia	Yes	No	Yes	
Hirsutism	No	No	No	
Hypertension	No	No	No	

FSH, follicle-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone; H, high; L, low.

FATs generally present with weight loss due to the weight loss-mediating effect of estrogens, especially in men [10]. However, a small percentage of cases of FATs are associated with weight gain [4]. While the weight gain could be independent of the FAT or part of an atypical tumor presentation, it is also a potential sign of SCS, or subtle cortisol hypersecretion from an adrenal tumor without elevated cortisol serum levels or the classic myriad of syndromes in Cushing syndrome [2]. The combination of unsuppressed cortisol on low-dose dexamethasone test, weight gain, atrophic nonneoplastic adrenal gland, and low ACTH makes SCS a possibility. This condition is found in 5–20% of adrenal incidentalomas, making it fairly common among adrenal tumors [2]. Confirmatory tests for SCS beyond low-dose dexamethasone and low ACTH include high-dose dexamethasone and no response of ACTH or cortisol to corticotropin-releasing hormone (CRH) stimulation [11]. A previous case of FAT with SCS has been reported similarly with gynecomastia, high estrogen, low ACTH, and upper normal cortisol that all resolved after surgery [9]. An alternative explanation proposed by the clinicians on this case for the unsuppressed cortisol on low-dose dexamethasone is high cortisol-binding globulin, and thus higher total cortisol, due to hypoalbuminemia. Additionally, due to estrogen's stimulatory effect on cortisol-binding globulin, the dexamethasone suppression test may show a false positive as a result of high estrogen levels.

The high adiposity in this patient could contribute to further exacerbating high estrogen levels caused by the FAT. This additive effect in estrogen levels could be part of the reason why this patient had persistent gynecomastia and reduced libido and erectile function, which are not always seen in other cases of FATs. The ventral hernia is likely unrelated directly to the tumor as one of the main risk factors of this condition is obesity. However, the risk could have been exacerbated by high estrogen levels as there is a causal link between estrogens and inguinal hernias demonstrated in mouse models [12].

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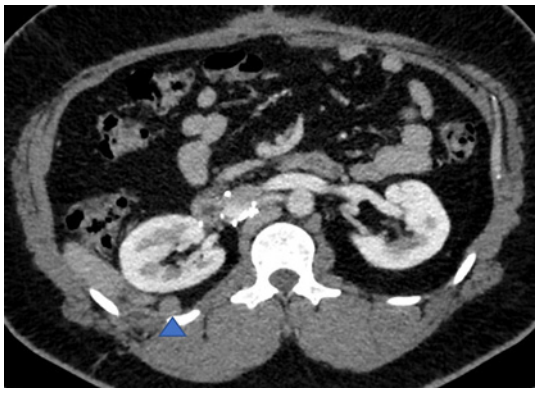

Fig. 3. Axial CT scan 18 months after surgery revealing a growing perinephric nodule (blue arrow) consistent with recurrent/locally metastatic disease (the inferior tip of the right hepatic lobe is seen lateral to the right kidney).

FATs typically present not only with high estrogen levels but also with low testosterone levels. There are a few proposed mechanisms for low testosterone levels with FATs including follicle-stimulating hormone/ luteinizing hormone inhibition due to negative feedback from estrogens, direct Leydig cell inhibition by estrogens, and estrogen-induced production of SHBG.

The Weiss score is an algorithm that classifies an adrenocortical tumor as benign or malignant based on histopathological findings. A point is gained for each of the following criteria: ≥5 mitotic findings per 50 high-power fields, clear cells ≤25%, presence of atypical mitoses, capsular invasion, necrosis, nuclear grade ≥3, >33% diffuse architecture, venous invasion, and sinusoidal invasion [13]. The modified Weiss score considers only the former five factors (mitotic findings, atypical mitoses, clear cells, capsular invasion, and necrosis), assigning 2 points for mitotic findings and clear cell criteria and 1 point for the rest. Both the Weiss score and modified Weiss score deem a neoplasm malignant with a score of ≥3 [13]. The Weiss score and its variants predict malignancy with a high degree of accuracy, allowing a malignant determination even in the absence of invasion on radiologic imaging.

Due to the aggressiveness of FATs, recurrence and metastasis are unfortunately not uncommon. Sites of metastasis can commonly include the liver, lungs, and pleura (necessitating frequent chest CT scans during surveillance), mesenteric lymph nodes, peritoneum, pancreas, kidney, and spleen [14].

Although radical adrenalectomy is the primary treatment for FATs and other adrenocortical carcinomas, medical treatment can be used in a first-line or adjuvant setting as well, although there is little clinical trial data to support their degree of efficacy [15]. Mitotane is the most widely used drug treatment in FATs as it has adrenolytic action and inhibits 11β-hydroxylase via free radical formation, both of which lower hormone production [4]. Ketoconazole can be used as well, especially with mixed secretion of cortisol [4]. Aromatase inhibitors could reduce estrogen secretion of FATs in theory, but their efficacy is still being determined [4]. Conventional chemotherapy, targeted chemotherapy, and radiotherapy are options as well [4].

This study comes with both strengths and limitations. One strength of the presented case includes consistent and thorough imaging of both the thoracic and abdominal regions on CT scan, allowing precise tracking of the recurrence and qualities of nodules. Another strength is the comprehensive set of diagnostic tests performed for this case including blood hormone laboratory values, CT, magnetic resonance imaging, gross tumor analysis, IHC, and histological analysis under light microscopy. However, because the management of the case is ongoing at the time of publication, it is difficult to draw conclusions about the prognosis or the efficacy of medical treatment in recurrent disease.

In conclusion, we present a case of an estrogen-secreting adrenocortical tumor with signs/symptoms of hyperestrogenism, numerous hepatic metastatic recurrences, SCS with progressive weight gain, and potentially complicating comorbidities such as obesity and steatosis. This case is a reminder of an important diagnostic consideration in male patients presenting with abdominal pain and feminizing attributes, as well as of the need for aggressive treatment and monitoring due to the high rate of recurrence.

Acknowledgments

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Statement of Ethics

Written informed consent was obtained by the patient for this publication and all accompanying images. There is no identifying information revealed in this publication. This retrospective review of patient data did not require ethical approval in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The manuscript was written by Joseph Rich. The manuscript was overseen and edited by Vinay Duddalwar, Phillip Cheng, Manju Aron, and Siamak Daneshmand. Radiologic images were acquired and annotated by Vinay Duddalwar. Pathologic images were acquired and annotated by Manju Aron.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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