# Feminizing adrenocortical carcinoma with distant metastases: can surgery be considered?

**Alessandro Fancellu, Antonio Pinna, Alberto Porcu**

**Unit of General Surgery 2, Department of Clinical and Experimental Medicine, University of Sassari, Italy**

## Abstract

Functioning adrenocortical carcinomas are rare diseases with dismal prognosis. A 41-year-old man presenting with gynecomastia had a giant feminizing adrenocortical carcinoma at stage IV. Although surgical resection was controversial, we removed the primary tumor to reduce the mass effects. He lived for 12 months with an acceptable quality of life. Gynecomastia may be the first sign of feminizing adrenal malignancies. Surgery may ameliorate the quality of life in selected patients with metastatic disease.

## Introduction

While adrenal adenomas are quite frequent in the general population, adrenal cortical carcinomas (ACCs) are rare malignancies affecting only 2 per million per year in the world population.[1,2] A bimodal age distribution has been recognized, with first peak in childhood (<5 years of age) and second peak in 4th-5th decade of life. Most of the ACCs are sporadic; however they may also arise within the context of familial or hereditary diseases.[2-4]

Although different studies have been undertaken in order to elucidate the molecular pathogenesis of sporadic ACCs, to date none of them has been proven to be completely exhaustive.[2,4] In particular, the genetic alterations characteristic of the adenoma-carcinoma sequence has not clearly established. To date, modification in three main molecular patterns has been identified: insulin-like growth factor (IGF)-2, the metabolic pathway Wnt/β-catenin and *TP53*.[4] ACCs can be either functioning (*i.e.* producing hormones of the adrenal cortex) or non-functioning. Adrenal malignancies are more likely to be functioning with respect to adenomas and can have different clinical presentations, depending on the type of hormonal secretion. In fact, patients may have symptoms of hypercortisolism, hyperaldosteronism, or sex hormone excess (either virilization or feminization), although mixed clinical features can be observed.[1,5]

Feminizing ACCs, *i.e.* malignant adrenal tumors causing features of estrogen excess, are an extremely rare cause of abdominal mass.

We herein present a case of a young man having a giant feminizing ACC with distant metastases, which posed serious management problems principally related to the burden of the primary tumor.

## Case Report

A 41-year-old gentleman presented complaining of a 6-month history of bilateral gynecomastia without galactorrhea, and a significant weight loss (8 kg in the last three months). In the last two months he also noticed abdominal and back pain, dyspepsia, and some episodes of vomiting, bloating and difficult passage of stools. The rest of his medical history was not relevant and he was on no medications. His family history revealed the presence of a 37-year-old sister with an established diagnosis of MEN1 (primary hyperparathyroidism, pancreatic gastrinoma, and prolactinoma) with germline mutation 894-9 G→A, and a 50-year-old brother affected by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma causing Cushing's disease. As the patient was in good health before the appearance of gynecomastia, he had previously refused to undergo laboratory and genetic testing. Laboratory tests showed: i) extremely high estradiol plasma levels (E2>500), together with undetectable gonadotropin levels and low testosterone; ii) the likely coexistence of Cushing's disease (hypercortisolemia with increased ACTH levels) (Table 1). In relation to the latter, an overnight dexamethasone suppression test (1 mg at 11.00 p.m.) was carried out, which failed to show serum cortisol suppression (19 μg/dL at 08.00 a.m.). On abdominal examination, a large, firm mass adherent to the deep layers was palpable in the left quadrants. The total body computed tomographic (CT) scan showed a large tumor of the left adrenal (25 cm in its maximum diameter) with colliquative areas infiltrating the left kidney (Figure 1), left renal vein thrombosis, and multiple liver and lung metastases. No pancreatic lesions were visible. Pelvic CT scan revealed no abnormality, while breast and testicular ultrasound confirmed the presence of gynecomastia and reduced testicular volume. Neck ultrasound showed neither enlarged parathyroid glands nor thyroid alterations. Pituitary magnetic resonance imaging and parathyroid sestamibi scan were also normal.

After a multidisciplinary discussion, it was decided to operate on the patient to remove the adrenal tumor, in an attempt to reduce the symptoms related to the mass, principally pain and recurrent subocclusive episodes. Before the operation, a medication with ketoconazole was started for hypercortisolemia; however, replacement of ketaconazole with metyrapone was necessary to normalize the cortisol levels. The patient underwent an exploratory celiotomy where a large encapsulated mass was encountered, displacing the kidney inferiorly and the distal pancreas and spleen superiorly. The mass and the left kidney were resected *en bloc*. On surgical exploration, the right adrenal also appeared increased in size, thus a bilateral adrenalectomy was performed. On gross pathology examination, the left adrenal tumor (which included approximately half of the left kidney, with diffusely infiltrated areas) weighed 3.3 kg, and measured 27×17×12 cm (Figure 2). The histological examination revealed an ACC with oncocytic changes with a Weiss score of 8 (Figure 3). Based on the histological finding, the laboratory tests, and the presence of distant metastases, we made the diagnosis of feminizing adrenocortical carcinoma at stage IV according to the American Joint Committee on Cancer (AJCC) classification. The right adrenal weighed 14 g and had aspects of cortical hyperplasia.

The postoperative course was uneventful, and the patient was discharged on postoperative day 12. He was given replacement therapy with hydrocortisone, fludrocortisone, and mitotane therapy without any important side effects. Six months after surgery, laboratory tests showed a normalization of cortisol and

Correspondence: Alessandro Fancellu, Unit of General Surgery 2 - Clinica Chirurgica, Department of Clinical and Experimental Medicine, University of Sassari, v.le San Pietro 43, 07100 Sassari, Italy.
Tel.: +39.079.228432 - Fax: +39.079 228394.
E-mail: afancel@uniss.it

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estrogens levels. Gynecomastia was markedly improved, and a mild reduction of the size of liver and lung metastasis was observed. He went on to live 12 months with an acceptable quality of life before dying from metastatic disease.

## Discussion and Conclusions

Feminizing ACCs are very rare, accounting for only 1-2% of all malignant neoplasms of adrenal cortex.[1] In 1994, Zayed reported fewer than 100 cases described in male sex.[6] Since then, only a few cases have been added to the literature.

Clinical features related to steroid excess occur in about 60% of ACCs, while feminizing symptoms due to estrogen secretion are extremely uncommon.[1,5]

The main presenting signs and symptoms of feminizing ACC are gynecomastia, testicular atrophy, decreased libido and impotence. In line with other reported cases, gynecomastia was the presenting symptom of ACC in our patient.[5,7] Gynecomastia recognizes various causes, being most commonly due to medications, imbalance between testosterone/estrogen levels, kidney failure, cirrhosis, and much more rarely to pituitary and adrenal tumors.[7] It has been suggested that feminizing symptoms can be linked to aberrant aromatization of adrenal androgens in estrogens, principally E1.[6] Feminization is often combined with hypercortisolism, as we observed in our patient.[6] While AACs are for the most part sporadic, they can occur as part of various familial tumor syndromes, such as MEN1, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Carney complex.[2,4] The familiar history of our patient denoted the presence of well-defined endocrine pathologies (MEN1 and ACTH-producing pituitary adenoma). Adrenal neoplasms are not commonly included in MEN1; however, non-functioning macronodular hyperplasia is observed in up to 40% of patients with MEN1 and, even rarely, ACCs can occur.[4] As a consequence, we investigated the existence of MEN1 syndrome in our patient, but the laboratory and imaging studies pre-

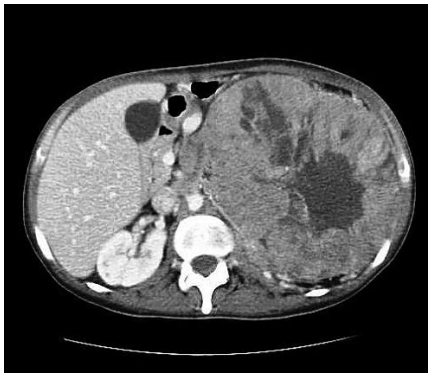

**Figure 1. Computed tomographic scan of the abdomen revealed a large tumor of the left adrenal (25 cm in its maximum diameter) with colliquative areas, occupying almost entirely the hemiabdomen.**

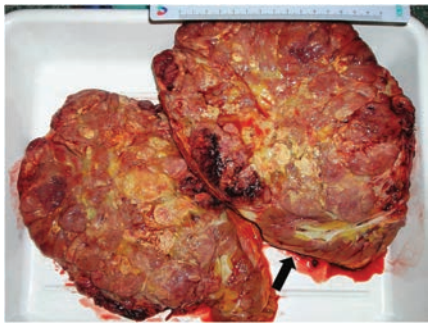

**Figure 2. The adrenal mass measured 25×17 cm, and appeared encapsulated, yellowish with extensive areas of necrosis and mucoid degeneration, encompassing the left kidney (black arrow).**

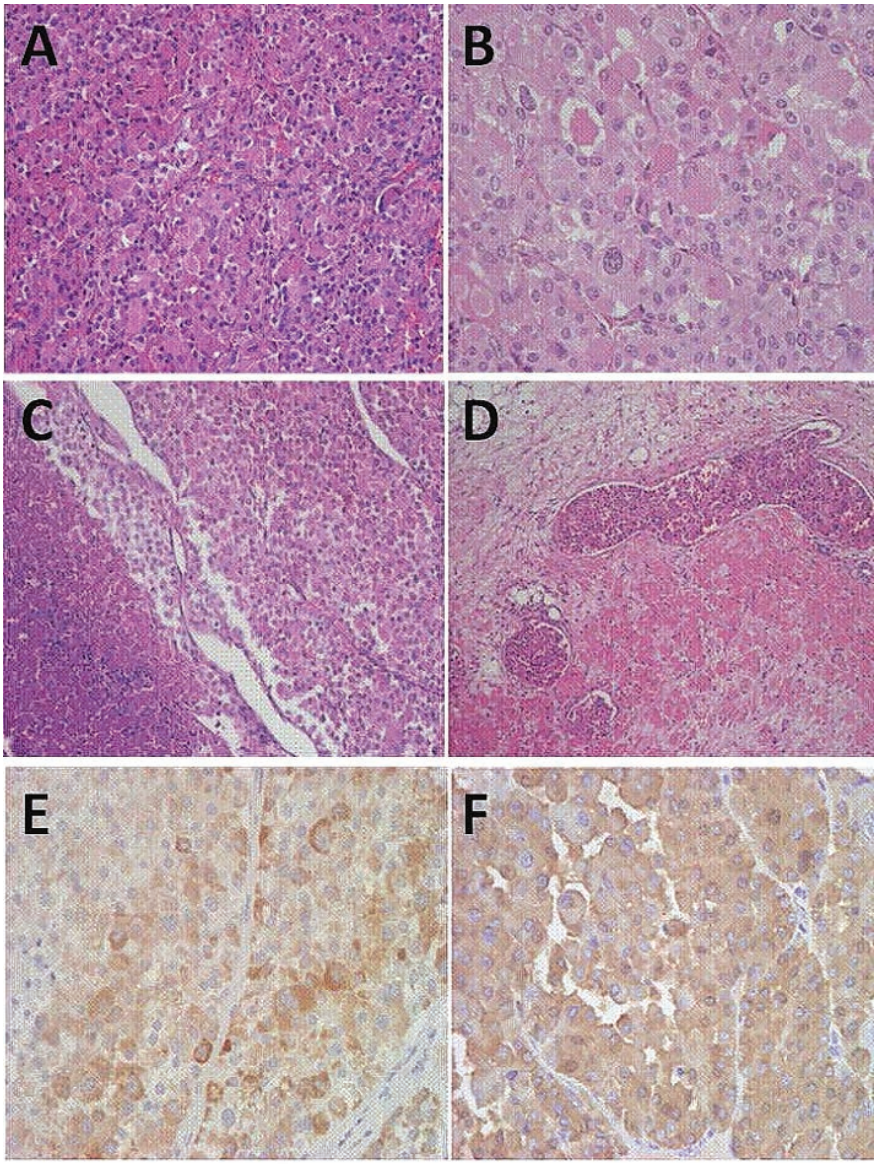


**Figure 3. Histological examination with standard hematoxylin and eosin showing a proliferation of large epithelial cells and pleomorphic oxyphil nuclei (A, 200×; B, 400×), with large areas of necrosis and endovascular embolization (C, 100×; D, 200×). Immunohistochemistry showing strong positivity for Melan-A and Synaptophysin in the tumor cells (E, 200×; F, 200×).**

vented us from confirming this hypothesis.

In the described case, invasion of surrounding organs and distant metastases defined the neoplasm as a carcinoma. However, differentiation between benign tumors (adenomas) of the adrenal cortex and ACCs is not always simple to achieve.[3] The likelihood of being malignant is very high for adrenal tumors producing sex hormones; in particular, feminization is quite consistent with malignancy more often than virilization.[5,8,9] As for the histological criteria, the model proposed by Weiss in 1984 still remains the most accurate and the one that best correlates with the prognosis of ACCs.[10] This model includes nine histological features distinguishing benign from malignant tumors. In our patient, 8 out of nine Weiss criteria were satisfied.

ACCs are notoriously aggressive tumors associated with poor prognosis. One cause for this finding is certainly the fact that many ACCs are detected at advanced stage. Preferred sites of metastatic spread are liver, lungs, and lymph nodes.

According to the literature, only 25-30% of patients present with stage I-II (disease confined to the adrenal), whereas about 70% present with stage III-IV (disease extending beyond the adrenal).[2] The two most important prognostic factors have been identified in stage at diagnosis and surgical radicality, though age, mitotic count, and Ki67 expression have also been considered.[3,9,11,12]

Historically, overall 5-year survival rates in patients with ACCs range between15% and 20%. In a study from the Memorial Sloan Kettering Cancer Center, patients with stage I-II disease and with III-IV disease had 5-year survival of 60% and 10%, respectively.[13] Complete surgical resection is the only potentially curative treatment, and nowadays remains the mainstay in the treatment of localized ACCs (stage I-III), even in patients with extension to adjacent organs and positive local lymph nodes. Five-year survival after surgical resection is approximately 40%.[12] Even patients who undergo radical surgery bear high risk (about 80%) of local relapse and metastases, which typically occur within 2 years.[2] When surgical removal is not achieved with radical intent, the prognosis is very poor (median survival <1 year).

Although the use of laparoscopic adrenalectomy for malignant AACs has been reported to be safe by some authors, there is a common agreement that open surgery should be preferred in this setting.[14,15]

Our patient had stage IV disease because of distant metastases (lungs and liver) and invasion of adjacent tissues.

In stage IV disease, chemotherapy or palliative cures have been the common options.[3] Surgical resection of metastatic ACC remains controversial, although surgery may have a role in metastatic ACCs providing that greater than 90% of the tumor and metastases can be removed, according to the National Comprehensive Cancer National guidelines.

**Table 1. Preoperative laboratory tests.**

| Test | Result | Unit | Normal values |
|---|---|---|---|
| LH | <0.1 | mUI/mL | 1.7-8.6 |
| FSH | <0.1 | mUI/mL | 1.5-12.6 |
| Estradiol | 577 | pg/mL | 7.63-42.6 |
| Prolactin | 26 | ng/mL | 2.5-17 |
| Testosterone | 5.98 | ng/mL | 2.8-8.0 |
| Free testosterone | 6.38 | pg/mL | 9-40 |
| DHEA-sulphate | >1000 | μg/mL | 89-427 |
| 17OH-progesterone | 13,762 | pg/mL | 400-3300 |
| CEA | 1.5 | ng/mL | 0-4.4 |
| α-fetoprotein | 18.8 | UI/mL | 0-5.8 |
| β-HCG | 0 | mUI/mL | 0-3 |
| PTH | 53 | pg/mL | 12-60 |
| Calcium | 10.02 | mg/dL | 8.10-10.40 |
| Phosphorus | 2.5 | mg/dL | 2.7-4.5 |
| 25hydroxy vitamin D | 55 | ng/mL | 40-60 |
| Cortisol (08.00 a.m.) | 25 | μg/mL | 5-23 |
| Cortisol (04. p.m.) | 22 | μg/mL | 3-16 |
| ACTH (08.00 a.m.) | 72 | pg/mL | 9-52 |
| Free urinary cortisol | 623±33.3 | μg/24/h | 4.3-176 |

LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEA, dehydroepiandrosterone; CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin; PTH, parathyroid hormone; ACTH, adrenocorticotropic hormone.

In the case described herein, the management decision was quite complex, as a result of the patient's young age, the presence of widespread disease and the local extension of the primary tumor. Following a multi-disciplinary approach, we decided to operate on the patient because of the local effects of tumor. Medical treatments had failed to alleviate these symptoms. The intention was obviously not to cure the patient with surgery, but to ameliorate his quality of life, and thus obtain a good palliation for mass effects and hormonal symptoms. To note, he lived with an acceptable quality of life for 12 months after the surgical removal of the adrenal mass. We can reasonably speculate that, in this case, surgery might have prolonged the overall patient survival.

Mitotane, alone or in combination with other chemiotherapics has historically been the main medicament used in the adjuvant setting following radical surgery as well as in metastatic disease. Its use is limited by significant, dose-dependent gastrointestinal and neurologic toxicity; in our case the mitotane therapy was quite well tolerated.

Survival rates from ACC have not substantially changed over the last 20 years, and systemic treatment, to date, is unsatisfactory.

The phase III FIRM-ACT trial comparing two different regimens in metastatic ACCs (etoposide, doxorubicin, cisplatin, and mitotane *versus* streptozotocin and mitotane) showed no difference between the two regimens in terms of overall survival (14.8 *vs* 12.0 months; P=0.07).[16]

Individualized therapies based on genomic and expression profiling of ACCs represent other promising perspectives.[2,14] As knowledge of the molecular mechanisms of ACCs continues to improve, it is likely that targeted therapies will improve survival outcomes in the near future. Numerous trials are investigating targeted agents such as epidermal growth factor inhibitors, antiangiogenic agents, tyrosine kinase inhibitors, IGF-1 inhibitors, and fibroblast growth factor receptor inhibitors.[2,14]

In our opinion, this report contains two principal points of interest. First, we emphasize the fact that feminizing ACC should be taken into account as a possible diagnosis in patients presenting with gynecomastia, especially when the common causes for this disorder have been ruled out. Second, surgery may have a role even in patients with functioning ACCs at stage IV, with the aim of improving quality of life by relieving symptoms of hormonal excess and mass effects.

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