

# Functional metastatic adrenocortical carcinoma in durable complete remission

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## Abstract

A 25-year-old woman, felt a dull pain in the right hypochondrium for a few months, accompanied by a change in her appearance with enlarged shoulders, swelling of the face, important hirsutism of the facial and genital trunk, profuse sweating and increase in muscle strength. ACT scan revealed a right adrenal mass of 15x17cm and multiple pulmonary nodules (>30 mostly basal lesions) and the laboratory report shows hypertestosteronemia and hyperprogesteronemia. Based on a clinical diagnosis of inoperable metastatic cortico-adrenal carcinoma, the patient received chemotherapy with doxorubicin, etoposide and cisplatin in combination with mitotane. A radiological assessment after 8 cycles of chemotherapy showed a marked decrease in the main mass and the lung lesions. A right surrenalectomy with partial resection and reconstruction of inferior vena cava was performed in March 2013. Adjuvant treatment with mitotane was continued for 2, 5 years. At present, the patient remains in complete remission since 4, 5 years. This case-report summarizes the novel treatments and the perspectives for adrenocortical carcinoma.

## Keywords

adrenal disorders; endocrine cancer

## Introduction

Adrenocortical carcinoma (ACC) is a rare disease with an estimated incidence of 0.7 new cases per million per year. Approximately 30-70% of the patients present with advanced disease and the estimated 5-year survival rate is less than 15%.

The incidence of the disease has a bimodal distribution with a peak in the first and fourth decade of life and a 2:1 ratio of women to men [1]. The majority of ACCs are sporadic but they may be part of hereditary tumor syndromes, associated with specific mutations of the germ lines (Li-Fraumeni syndrome, Lynch's syndrome or MEN1 syndrome) [2]. ACC remain a disease with a very poor prognosis, particular if metastatic at presentation. Patients with localized disease have a 5-year survival of 60-80%, those with locally advanced disease 35-50% and those with metastatic disease 13-28%.

Among symptoms in its presentation, virilisation is the most common, with Cushing's syndrome and precocious puberty following in frequency. In a few cases, feminization and Conn syndrome

(mineralocorticoid excess) can be present as well as hypersecretion of catecholamines. In case of non-functional tumours (about 40%) the first calling symptom is an abdominal pain. Sometimes patients may be asymptomatic and diagnosis can be made incidentally.

Based on a randomized controlled clinical trial the chemotherapy regimen based on cisplatin-doxorubicin-etoposide in combination with mitotane has become standard of care. This regimen produces 23% of partial responses and the overall survival is about 14 months. Much effort has been done to understand the mechanism of carcinogenesis in ACC and to find signal transduction pathway aberrations that could be used as therapeutic targets to develop new drugs. Unfortunately no one of them has reached to a solid conclusion of a new therapeutic effective option, which could be the new standard for the ACC.

We report a case of a young woman, presenting with a locally advanced ACC as well as massive pulmonary metastasis at diagnosis, who is in complete remission 5 years after multimodal treatment.

## Case Presentation

A 25-year-old woman, in previous good health and no family history for cancer, felt a dull pain in the right hypochondrium for a few months. At the same time she noted a change in her appearance with enlarged shoulders and swelling of the face, important hirsutism of the facial and genital trunk resembling a male pilositis, profuse sweating as well as an increase in muscle strength. She consulted her physician, who detects a hypertestosteronemia of 43 nmol/l [normal range 0.35-3.12 nmol/l] and hyperprogesteronemia of 60.5 nmol/l [normal range 0.79-1.71 nmol/l]; prolactin, oestradiol, LH, FSH, TSH were in normal values. ACT scan revealed a right supra-renal mass of 15x17cm, invading inferior venacava and the right part of liver, as well as multiple pulmonary nodules (>30 mostly basal lesions) (**Figure 1**). There was a venacava thrombus up to the diaphragm and the patient had a clinically relevant pulmonary embolism just before starting treatment.

Based on a clinical diagnosis (no biopsy) of inoperable metastatic cortico-adrenal carcinoma, the patient received chemotherapy with doxorubicin (40 mg/m<sup>2</sup> on day 1, etoposide 100 mg/m<sup>2</sup> from day 2 to day 4 and cisplatin 30 mg/m<sup>2</sup> from day 3 to day 4, every 3 weeks in combination with mitotane which was started at a dose of 3g per day, aiming at its plasma concentration between 14 and 20 mg/lt [3,4]. 8 cycles were administered between September 2012 and February 2013.

A radiological assessment after the end of the 8 cycles showed a marked decrease in the main mass (9 cm in the greater axis compared to 17 cm) and four millimetric lung lesions. A right surrenalectomy with partial resection and reconstruction of vena cava was performed in March 2013 (collaboration of visceral and cardiac surgery).

The anatomo-pathological report confirms the clinical diagnosis, with a 9 cm, largely (90%) necrotic and fibrosated mass, showing tumor cells of variable size, with high nuclear pleomorphism, diffuse architecture, high mitotic rate and venous invasion (**Figure 2**), fulfilling at least 3 out of 9 criteria in Weiss diagnostic histopathological system [5]. The immunohistochemical examination that are positive for Inhibin, Mephalan-A and Chromogranin and negative for CEA and Cytokeratin AE1/AE3.

Adjuvant treatment with mitotane was continued until February 2015 (2.5 years in total) and was complicated because of headache associated with nausea and fatigue.

Since the PET. CT of 10.2013, the control imaging showed that the disease is in complete remission without any sign of recurrence. At present, the patient is monitored by CT-scan every six months (**figure 3**). She is undergoing continuous corticosteroid replacement therapy.

## Discussion

In recent years a major advance has been done in the understanding of the genetics of ACC. In recent years a major advance has been made in the understanding of the genetics of ACC by using the next generation sequencing to explore the genomic landscape, showing tumour biological and genetic heterogeneity.

The development of effective targeted therapies for this disease, as well as the construction of a valid prognostic scale based on clinico-pathological and genomic characteristics of predictive models, are also hampered by the rarity of this tumor [6].

The only potentially curative treatment for cortical-adrenal carcinoma remains (in case of resectability) surgical resection [7]. Relapses after surgery are frequent and 50% of patients are already metastatic in the diagnosis.

Adjuvant treatment with mitotane showed an important improvement in progression-free survival. The optimal duration of adjuvant treatment with mitotane is not clearly established. For patients at high risk of recurrence, it is proposed to treat them for 5 years, or if not possible, according to the tolerance, preferentially for a minimum of 2-3 years [8].

The surgical approach could also be considered for patients who present with resectable metastatic lesions, as well as some selected patients, for the control of the symptoms in a context of hormonal excess.

The addition of radiotherapy therapy is suggested postoperatively for patients with partially resected mass or with a high-grade tumor by some studies but not universally accepted. No benefit of radiotherapy was demonstrated for cases with advanced/metastatic disease [9].

Glycocorticoid substitution is essential after resection of the tumor. It should also be administered to patients with a non-cortico-secreting tumor, in association with mitotane due to its adrenolytic activity. Hydrocortisone is used for this reason mainly in relation to dexamethasone. Mitotane can also cause an aldosterone deficiency. In this case the treatment of choice remains fludrocortisone.

For patients with irresectable disease, treatment with mitotane in combination with etoposide-doxorubicin-cisplatin chemotherapy are proposed (better response and progression-free survival compared to the combination of the triplet of the above-mentioned chemotherapy with streptozocin) [10]. Nonetheless it is associated with serious adverse events in greater than 50% of patients including myelosuppression, cardiovascular or thromboembolic events, infection, neurotoxicity and general health deterioration.

For patients with hypercortisolism (not controlled by mitotane or those who do not receive it), the use of metyrapone in combination with ketoconazole may be proposed.

Percutaneous radiofrequency ablation (RFA) may provide short-term local control in the context of an irresectable tumor, particularly for those who measure less than 5 cm in size [11].

For the palliation of the symptoms of a locally advanced or metastatic disease radiotherapy has shown a good efficiency.

### **New and experimental approaches - Targeted therapies**

Targeted therapies are tested in the context of clinical trials, often after progression of the disease beyond standard treatments (mitotane and chemotherapy).

The majority of ACC tumor cells (up to 80%) over express IGF2 (insulin-like growth factor type 2) which is known to exert its effects by binding to the IGF-1 receptor and promoting activation of the PI3K/AKT signaling pathway. A Phase I/II study using cixutumumab antibody (a humanized monoclonal antibody against IGF-1) showed unfortunately very limited efficacy, with some partial responses and stabilization of the disease in a small number of patients [12]. In the same way linsitinib (OSI-906) did not increase overall survival in a double-blind, randomized, phase III study [13].

A rescue treatment with erlotinib (an EGFR inhibitor), in combination with gemcitabine showed a minor benefit in a serie of 10 patients with only 1 patient presenting a minimal response and the remainders a progression of the disease [14].

Another Phase II study, combining cixutumumab and temsirolimus (mTOR inhibitor), showed a 50% stability of the disease, a result that remains promising for combining-molecules strategies and a possible important role for mTOR inhibitors. On the other hand, everolimus (another mTOR inhibitor) alone did not show a signal of clinical activity in another study with 4 patients [15].

Despite the fact that Vascular Endothelial Growth Factor (VEGF) is overexpressed in the adrenocortical-carcinoma cellules membrane, a study of 10 patients with advanced disease showed no significative response of bevacizumab in combination with capecitabine [16].

More recently, a very limited therapeutic activity has been demonstrated for the selective inhibitor of VEGFR, axitinib, in a study of 13 patients [17]. Sorafenib, a tyrosine kinase receptor inhibitor (VEGFR2, VEGFR3 and PDGFR) was investigated in a Phase II study in combination with paclitaxel, but was unable to demonstrate clinical activity [18].

### **Immunotherapy**

The antineoplastic activity of immunotherapy (checkpoints inhibitors anti-CTLA-4 and anti-PD-1 antibodies) for the treatment of solid tumors such as melanoma and non-small cell lung cancer has driven the interest to explore its potential efficacy in ACC. The membrane of cancer cells as well as tumor-infiltrating mononuclear cells were evaluated for PD-L1 expression by immunohistochemistry in 27 patients with resected ACC; there was no correlation demonstrated between PD-L1 expression and overall survival, higher tumor stage or grade at diagnosis [19].

Some Phase I and II studies using molecules (avelumab and pembrolizumab) that target the PD-L1 (programmed cell death ligand 1) are underway (**table 1**) as well as another one using interleukin-12 as an immunomodulator in combination with trastuzumab (humanized antibody binding to the epidermal growth factor receptor 2) which remains in the experimental phase, without having proved for the moment a significant clinical effectiveness [20,21].

The role of the immune control points in the pathophysiology of ACC and their possible therapeutic involvement remains to be determined. Importantly, several studies have explored the genomic landscape of this rare malignancy using next generation sequencing approaches. Some mutations in several genes, such as ZNRF3 (20%), CTNNB1 (14%), TP53 (14%), CDKN2A (11%), RB1 (5%), MEN (16%), DAXX (5%), MED12 (3%) and TERT (5%), have been identified but without any therapeutic potential for the moment. Comprehensive genomic profiling of ACC tumor samples is underway through “The Cancer Genome Atlas” program and final results are expected in the near future that will certainly add important information to guide future drug development.

## Conclusion

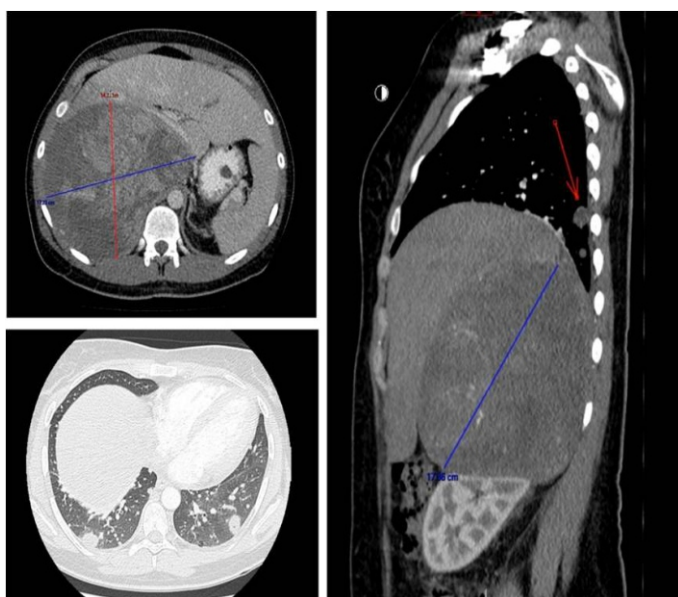
Here we report an extreme rare of prolonged complete remission of a largely metastatic ACC treated with poly-chemotherapy and surgery and adjuvant treatment.

For the moment chemotherapy and mitotane remain the standard of care for the treatment of locally advanced or metastatic disease. New studies are necessary in order to improve the effectiveness of the available treatments which are unfortunately still unsatisfactory for the majority of patients. Despite the rarity of the disease randomized controlled trials are feasible and new molecular findings pave the way to more effective treatments.

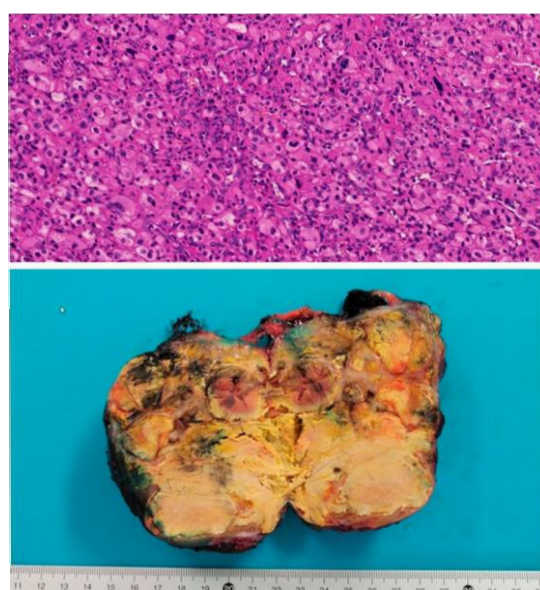
## Learning Points

- ▶ Adrenocortical carcinoma is a rare disease with a poor prognosis in an advanced stage.
- ▶ Surgery remains (in case of resectability) the only potentially curative treatment.
- ▶ Addition of adjuvant mitotane shows an important improvement in progression free survival.
- ▶ For irresectable disease the combination cisplatin-doxorubicin-etoposide with mitotane showed a significant prolongation of progression-free survival over streptozozin-mitotane and is now regarded as standard of care for metastatic disease.

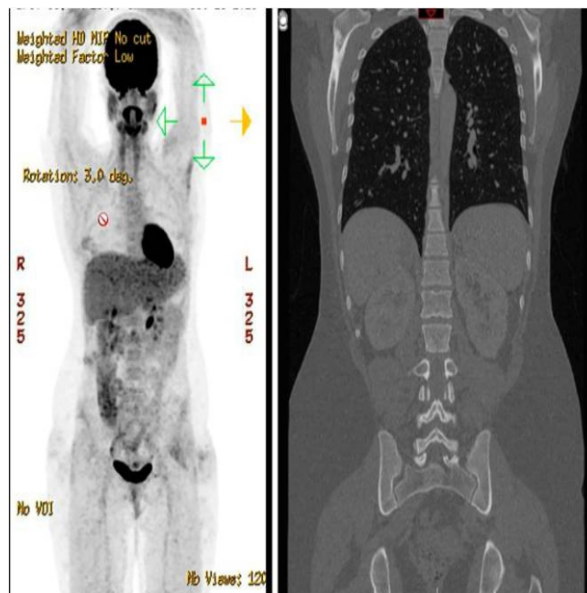
## Figures



**Figure 1:** Initial CT-scan: voluminous right supra-renal mass of 17x15 cm. Multiple pulmonary nodules.



**Figure 2:** Initial CT-scan: voluminous right supra-renal mass of 17x15 cm. Multiple pulmonary nodules.



**Figure 3:** Radiologic images that show the complete remission (PET-CT the 15.10.2013 and CT-scan the 27.04.2017).

## Table

**Table 1 :** Current ongoing and recruiting studies on advanced ACC at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Drug	Target	Type	Study Population	Clinicaltrials.gov ID
Abiraterone Acetate	17 $\alpha$ hydroxylase/C17, 20-lyase	Interventional	ACC	NCT03145285
Cytoreductive surgery Cisplatin (HIPEC)	x	Phase II	ACC	NCT03127774
Cytoreductive surgery Cisplatin (HIPEC)	x	Phase II	ACC	NCT01833832
MITOTANE	x	Phase II	ACC	NCT00777244
ATR-101	Acyl coenzymeA:cholesterol O-acyltransferase	Phase I	ACC	NCT01898715
Pembrolizumab	Programmed cell death 1 inhibitor	Phase II	ACC	NCT02673333
Nivolumab	Programmed cell death 1 inhibitor	Phase II	ACC	NCT02720484
Avelumab	Programmed cell death ligand-1 inhibitor	Phase I	Solid tumors	NCT01772004
Nivolumab and Ipilimumab	PD-1 and CTLA-4	Interventional	Rare tumors	NCT02834013

Accessed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) on November 12th, 2017  
 HIPEC: Heated Intraperitoneal Peritoneal Chemotherapy

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