Etomidate as an emergency treatment for uncontrolled hypercortisolism in metastatic adrenocortical carcinoma

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INTRODUCTION

Adrenocortical carcinoma is a rare malignancy that may cause excessive secretion of cortisol or androgens or both, in 50% of the cases. The incidence is 1-2/10^6 cases per year. The prognosis is poor with a 5-year survival rate of 50%, dropping down to 15% in case of metastatic disease. The treatment could be challenging, especially in advanced or metastatic cases [1, 2, 3].

CASE REPORT

A 26-year-old woman was diagnosed with a multiple metastatic adrenocortical carcinoma after referred to our clinic. Her medical history was unremarkable except from an autoimmune hypothyroidism and a dysmenorrhea, for which she was taking a contraceptive pill for many years. A few months prior to diagnosis, she developed a clinical severe Cushing's syndrome with signs of virilisation (**Figure 1**).

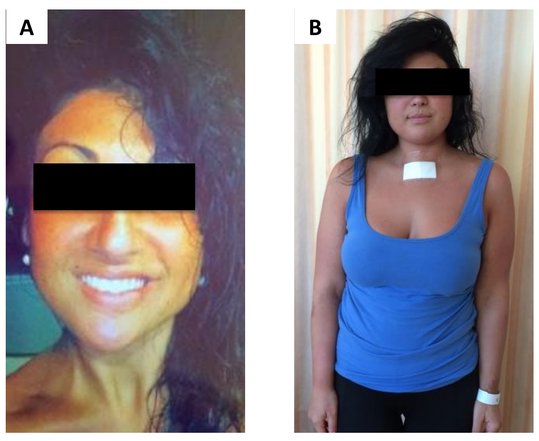


Figure 1: patient's photos

A: in november 2015

B: in january 2016

The first hormonal evaluation is shown in **Table 1**.

Hormones	Values	Normal ranges	Units
FSH	<1	-	U/L
LH	<1	-	U/L
Oestradiol	<20	-	ng/L
Progesterone	3.8	-	µg/mL
17OH-Progesterone	7.2	-	ng/mL
SHBG	50	32-130	nmol/L
DHEA-s	8047	900-3500	ng/mL
Total Testosterone	16	0.29-1.7	nmol/L
Free Testosterone Index	32	0.30-5.6	-
Cortisol (8:00 AM)	484	70-250	ng/mL
ACTH	<5	6-60	pg/mL
Urinary Free Cortisol (UFC)	402	10-110	µg/24h

The radiological exploration revealed a voluminous mass (9 cm) in the left adrenal gland and multiples metastasis in lymph nodes, liver, lungs and bones (**Figure 2**).

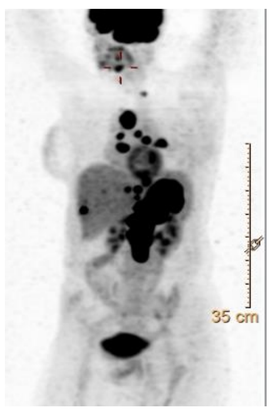


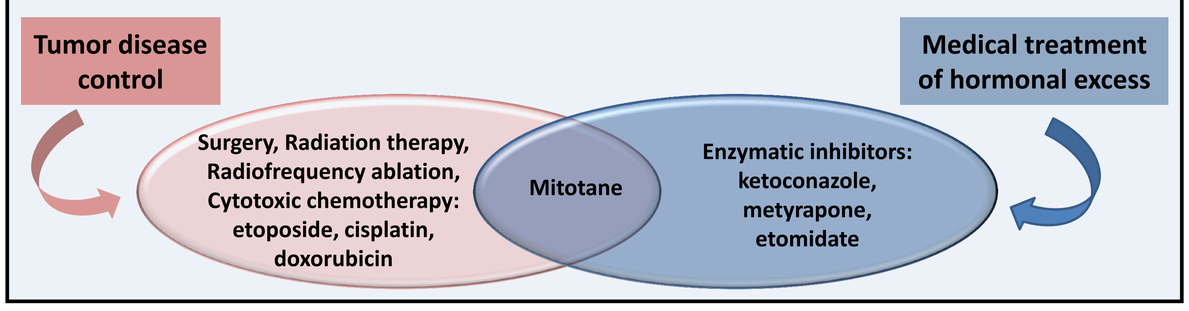
Figure 2: FDG-PET scanner

Image showing a strong avidity for the marker in the left adrenal gland, in supra- and infra-diaphragmatic lymph nodes and in the liver

Following the ENSAT (European Network for the Study of Adrenal Tumors) classification, the tumor was classified as stage IV because of the presence of distant metastasis (**Table 2**).

STAGE	ENSAT classification	T: tumor N: lymph node M: metastasis
I	T1, N0, M0	T1: tumor size ≤5 cm, N0: no positive lymph nodes, M0: no distant metastasis
II	T2, N0, M0	T2: tumor size ≥5 cm
III	T3-4, N0, M0 T1-2, N1, M0	T3: tumor invasion in adjacent organs, vena cava or renal vein N1: positive lymph node(s)
IV	any M1	M1: presence of distqnt metastasis
Fassnacht et al. Cancer 115, 242-250 (2009)		

Therapeutic management of adrenal carcinoma is based on the local therapy of the tumor disease and on the medical treatment of hormone excess.



Treatment and follow-up

Mitotane and Ketoconazole combination therapy was first initiated. A surgical resection of the left adrenal gland was also performed to control the severe Cushing's syndrome. Cisplatin-Etoposide chemotherapy was started 20 days later postoperatively.

Due to the persistence of life-threatening hypercortisolism, an alternative treatment with Etomidate was proposed (**Figure 3**).

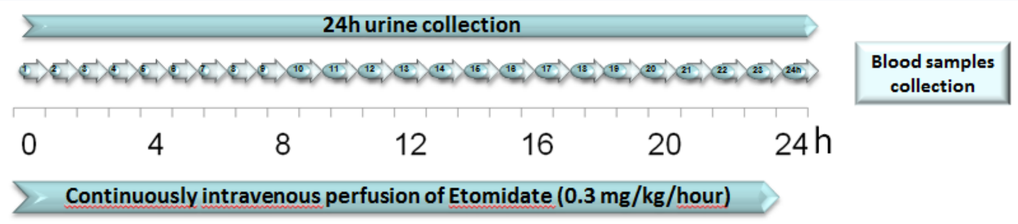


Figure 3: A 24-hour continuous intravenous infusion of etomidate at the dose of 0.3mg/kg/hour was administrated under close observation in the intensive care unit [4]. Blood samples for cortisol measurement were collected each hour to follow adrenal cortisol production inhibition. 24-h urine collection for urinary free cortisol measurement was also performed during treatment.

The inhibition of the adrenal cortisol production was rapid (**Figure 4**) and the urinary free cortisol (UFC) decreased to less than 5-fold the upper limit of normal range within 8 hours (**Figure 5**).

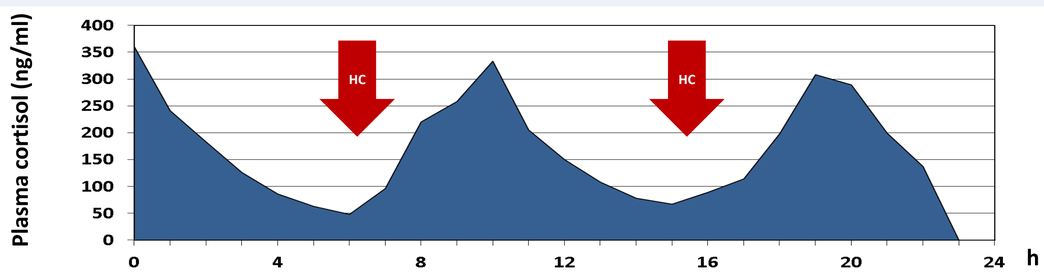


Figure 4: Plasma cortisol decreased rapidly during etomidate treatment at 0.3 mg/kg/h. Six hours after beginning of etomidate treatment, plasma cortisol reached a value of 48 ng/ml. A preventive substitution by oral hydrocortisone (HC) at the dose of 20mg was introduced during etomidate perfusion.

One month later, the medical evaluation after 2 cycles of chemotherapy showed normalized UFC and regression of metastasis, with good results persisting over the follow-up (**Figure 5**).

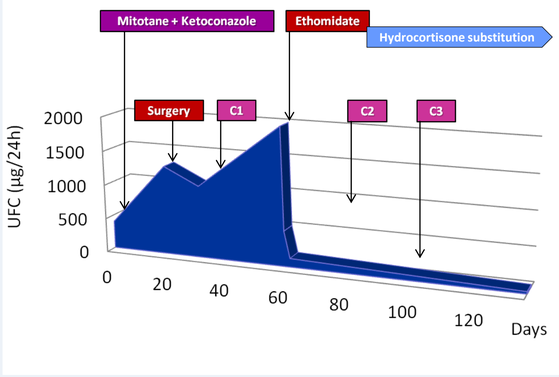


Figure 5: Urinary Free Cortisol (UFC) measurements from diagnosis (Day 0). Graphic shows an aggravation of the hypercortisolism despite the initiation of a treatment with multiple enzymatic inhibitors and surgery. Etomidate treatment allows a rapid control of the severe hypercortisolism waiting for efficacy of chemotherapy (C1, C2, C3). Patient was even substituted by oral hydrocortisone (HC) after etomidate treatment.

DISCUSSION

Several therapeutic agents are recommended for the control of cortisol hypersecretion. In patients with life threatening hypercortisolism, metyrapone-ketoconazole combination therapy is very effective and may rapidly improve the patient's condition before surgery or chemotherapy [4]. Etomidate, mostly known as anaesthetic, is a strong enzymatic inhibitor of the 11β-hydroxylase implicated in the last step of the adrenal cortisol steroidogenesis [2]. The suppression of serum cortisol levels takes place within 10 hours from the onset of the drug administration and persists for 24h to 4 days after its discontinuation. Rarely its suppressive action can exceed the 10 days. Etomidate is a very useful additional therapy for the control of Cushing's syndrome particularly when oral therapy is either not tolerated or not rapidly available. The need for close monitoring limits its use to very severe cases. The dose must be individualized regarding the clinical status of the patient [5, 6]. Very limited data on the use of Etomidate in severe hypercortisolism are available in the literature.

CONCLUSION

This case illustrates the utility and efficacy of etomidate in the acute phase of hypercortisolism while waiting for efficacy of other adrenal-directed therapies and chemotherapy.

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