

Unrecognized androgen secreting huge adrenocortical carcinoma in need of urgent surgery

Gianfilippo Nifosi, Freddy Mboti, Yves Dernier, Ruth Dutmann

ABSTRACT

Introduction: The adrenocortical carcinoma is a rare aggressive endocrine malignancy that presents itself as an abdominal mass, symptomatic or incidental, often locally advanced or metastatic disease. Surgical resection when possible is the treatment of choice and margin-free resection is the most important prognostic factor for long survival. **Case Report:** In this paper, we describe the case of a woman of 58-year-old, bearer of an enormous androgen-secreting cancer, which has gone unnoticed for years, presenting with abdominal hemorrhagic syndrome which required surgical resection in emergency. **Conclusion:** In view of prognostic factors, we decided to complete the radical treatment with local radiotherapy and adjuvant mitotane.

Keywords: Aggressive endocrine cancer, Cancer surgery, Emergency

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INTRODUCTION

The adrenocortical carcinoma (ACC) is a rare aggressive endocrine cancer, with an incidence of 0.7-2 / 1,000,000, representing 0.2% of all malignancies. It has a slight female prevalence and a typical bimodal trend concerning the childhood, and the first and the fifth decades of life [1]. The most cases occur sporadically, as far as is possible that it is part of complex hereditary syndromes, for example: Li Fraumeni, Lynch and Beckwith-Wiedemann. In many cases its diagnosis is incidental, in the course of radiological investigations for abdominal discomfort. In 60% of cases, it secretes adrenal and/or sexual hormones, causing various syndromes, such as cushing/virilization (35%), cushing (30%), virilization (20%) or feminization (10%) [2].

In childhood, more than 90% is secreting. This cancer is manifested with abdominal masses of sometimes considerable dimensions and weight, encapsulated, with aspects of necrosis and/or hemorrhage, occasionally causing compression and bleeding abdominal disorders [3]. Its clinical presentation as acute abdomen is not very frequent [4]. Generally, it has poor prognosis, also because the diagnosis is often delayed. The risk of recurrence is 70–80%, even when it is excised completely, depending on clinical and histopathological prognostic factors [5]. As regards the currently used system for staging is that

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of European Network for the study of Adrenal Tumors (ENSAT) [6] that distinguishes four stages (Table 1). The treatment consists of a multimodal approach, i.e., surgery, radiotherapy and medical.

In this paper, we present a case of ACC secreting androgens and less cortisol, particular for the huge size and the clinical presentation which required urgent surgical treatment.

CASE REPORT

A 58-year-old female presented to the emergency department accusing several days intense asthenia, and abdominal pain. Medical history was positive for arterial hypertension and hypothyroidism substituted. The clinical examination showed pallor, hypotension, presence of abdominal mass, and signs of virilization. The laboratory examinations highlighted normocytic-normochromic anemia, neutrophilic leukocytosis, inflammatory syndrome, abnormal liver tests and increase of lactate dehydrogenase (LDH). Hormonal tests showed an overproduction of cortisol and androgen hormones (Table 2). Aldosterone, thyroid hormone and adrenocorticotrophic hormone were normal. The urinary excretion of catecholamine, cortisol, vanillylmandelic and 5-hydroxyindolacetic acid were normal. An abdominal scan with contrast highlighted a huge complex heterogeneous mass of 19.5x19x17 mm at left hypochondrium, originating from retro-pancreatic space, displacing pancreas and mesentery front, and spleen laterally. Active bleeding was noted in the lower internal part of the mass (Figure 1). Contrast-enhanced magnetic resonance confirmed encapsulated large mass in the left adrenal space with a necrotic sides, partially hemorrhagic share, of neoplastic nature (Figure 2). Positron emission tomography-computed revealed a bulky retropancreatic mass, hypermetabolic in its periphery and the septa, which contained large hypometabolic areas of necrotic or liquid nature, and exclude the presence of metastases. It was realized in emergency an angioembolization of nurse artery of masse departing from a common trunk with the diaphragmatic arteries. Once hemodynamically stabilized, the patient was operated. Given the impossibility of finding a cleavage plane to the level of the pre-renal fascia, and the invasion of renal vessels, the mass is removed together with the left kidney. Unfortunately, during separation of adhesions between the spleen and the pancreas, it was noticed a tumor capsular effraction at level of his hematoma.

The macroscopic anatomical aspect (Figure 3) was a yellowish tumor of 20 cm of major axis with a weight of 2335 grams, largely necrotic and hemorrhagic with capsular effraction. Histological examination revealed the presence of an aggressive ACC with microvascular invasion, presence of atypia and marked fibrous bands, but no frequent mitosis (Ki 67: 5%) (Figure 4). The left kidney showed signs of infarction and

Table 1: Staging system for ACCs

ENSAT stage	T	N	M
I	1	0	0
II	2	0	0
III	1,2	1	0
	3,4	0,1	0
IV	1-4	0,1	1

ENSAT: European Network for the study of Adrenal Tumors. Tumors are classified as follows: T1 tumor ≤ 5 cm, T2 tumor > 5 cm, T3 tumor infiltration into surrounding (fat) tissue, T4 tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein, N0 no spread into nearby lymph nodes, N1 positive lymph node(s), M0 no distant metastasis, M1 presence of distant metastasis

Table 2: Dose hormones before and after surgery

	Preoperative	Postoperative	Range
Testosterone (nmol/L)	6.77	0.60	0.29–1.67
DHEA-S (nmol/L)	> 27.00	1.40	0.51–5.56
Testosterone index (nmol/L)	21.69	0.84	0.30–5.60
ACTH (pg/ml)	3.45	7.56	6–60
Cortisol 8 h. (nmol/L)	756.6	615.7	166–507

DHEA-S: dehydroepiandrosterone sulfate

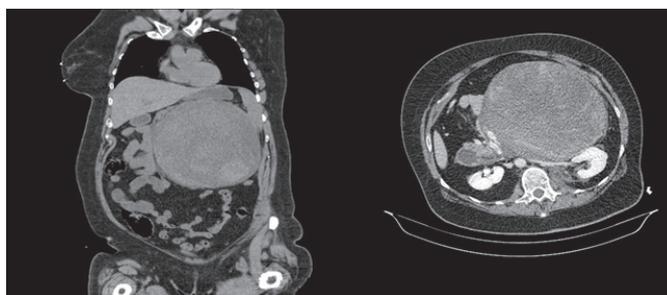


Figure 1: Abdominal computed tomography scan coronal and transverse plane.

two angiomyolipomas. The tumor cells were partially immunohistochemically positive for inhibin and CK AE 1/3, but negative for chromogranin.

DISCUSSION

Being a rare malignancy, there is no strong evidence of treatment standards for adrenocortical carcinoma (ACC). It is known that surgical resection with free margins is the optimal treatment for localized disease.

There are less certainty for complementary therapies for locally advanced or metastatic disease, since the risk of recurrence after resection is approximately 70–80%. Unfortunately, ACC prognosis is poor and it depends on the presentation stage. The five-year survival for stage I-II comes at 50–60%, but drops to 25% in stage III and is 0% in stage IV. Therefore, the identification of prognostic

factors was a key point. The first histopathological prognostic factors were identified by Weiss in 1984 [7] (Table 3).

It has clear evidence of malignancy when three or more criteria are present. Important prognostic factors are the histopathologic proliferation index. Ki67 is a powerful prognostic marker in both localized and metastatic ACC. Moreover, a mitotic count > 20 mitoses/50 HPF defines a “high grade ACC”. All authors agree in considering the presentation stage, pathological grade and completeness of resection as the most powerful prognostic factors. Bilimoria [8], studying a large number of patients (3928) identified some negative factors of recurrence and survival like: patients of aged over 55 years, R1 surgical margins, resection of adjacent organs, invaded lymph nodes and distant metastases. The R0 patients had a average survival of 51.2 months, conversely those R+ only 7.0 months. In other studies, advanced tumor stage, size, intralesional hemorrhage, hormonal secretion and a high K1 67 were considered to be negative prognostic factors [9]. Intraoperatively, maintaining capsule integrity and vascular control, total resection of the invaded organs and prevention of tumor spillage, are technical factors of fundamental importance to ensure long-term survival. For this reason the open transabdominal approach is preferable to that laparoscopic [10, 11].

Recently, in a multicenter study of adrenocortical carcinoma patients undergoing R0 resection, lymphadenectomy was independently associated with improved overall survival [12]. The treatment of complete resection (R0) “low-intermediate risk” (stage I-II, Ki 67 ≤ 10%) is adjuvant mitotane [13], while for incomplete resection (R+) or “high risk” (stage III, Ki 67 > 10%) is mitotane +/- radiotherapy. Radiotherapy in the adjuvant setting must be considered for large tumors, vascular invasion and Ki 67 ≥ 10% [14]. For metastatic disease, the best treatment is represented by the association of mitotane with etoposide-cisplatin-doxorubicin (M-EDP) [15].

Recently, research has focused on the identification of prognostic factors of genetic and molecular order. Different genomic approaches clarified that three pathways are especially important in the pathogenesis

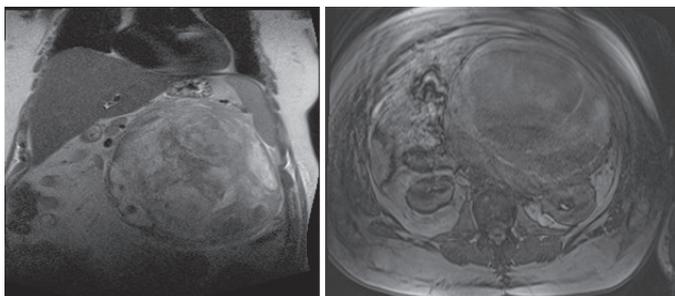


Figure 2: Contrast-enhanced magnetic resonance image coronal and transverse plane.



Figure 3: Macroscopic appearance.

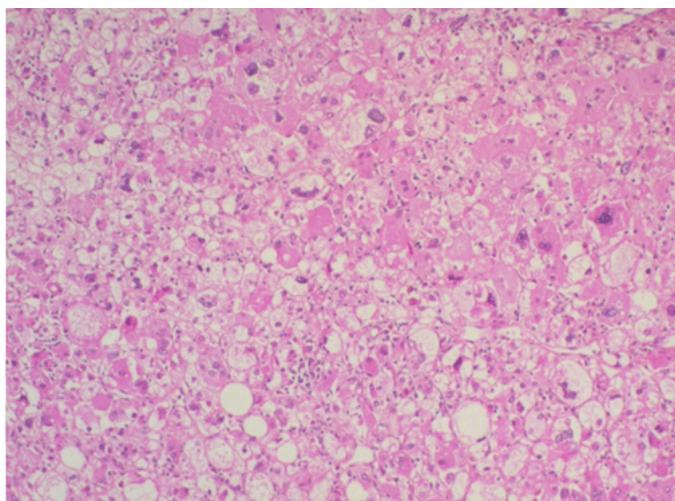


Figure 4: Adrenocortical carcinoma with microvascular invasion (H&E stain, x400) .

Table 3: Weiss score

High nuclear grade
Number of mitoses
Presence of abnormal mitosis
Clear cells > 25%
Diffuse architecture ≤ 33% of surface
Necrosis
Venous invasion
Sinusoidal invasion
Capsular invasion

of the ACC: over-expression of IGF2 (located on 11p15), WNT/ β -catenin mutations and inactivating mutations of TP53 [16]. The genetic approach has identified in the Zinc and ring finger protein 3 (ZNRFP3 or SNAIL) a transcription factor whose expression correlates with stage and proliferative activity and negatively with overall survival. Overexpression of steroidogenic factor 1(SF1) is associated with a poor prognosis regardless of the stage of disease. A correlation between the methylation-sensitive genes (GoS2, H19, and NDRG2 PLAGLI) and poor prognosis has been reported. Finally, the study of circulating miRNAs as brought the following results: a high level of miR-483-5p and a low level of miR-195 which were correlated with shorter recurrence-free and overall survival [17]. All these researches have been the starting point for testing targeted agents and immunotherapy in the treatment of metastatic disease [18].

CONCLUSION

The case presented lends itself to some final considerations. Its uniqueness lies in the presentation with secreting advanced disease (stage III, T4NoMo) and considerable size which, together with the hemorrhagic syndrome, needed an urgent surgery, which unfortunately resulted in the capsular rupture and tumor spilling. For this reason we decided to treat our patient with adjuvant radiotherapy and mitotane.

Author Contributions

Gianfilippo Nifosi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Freddy Mboti – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Yves Dernier – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Ruth Dutmann – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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