

Adrenocortical carcinoma, case report

Carcinoma corticoadrenal, reporte de caso

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Abstract

The adrenocortical carcinoma is rare and aggressive. It has a bimodal presentation, predominantly female, > 20% of cases will be diagnosed incidentally. 43-year-old male, with colic pain in the left flank, weight loss and intermittent fever. Computed tomography with a tumor on the left adrenal with liver metastases, block resection surgery was performed, pathological report of adrenocortical carcinoma with a 7 points of Weiss score and Ki67 40%. Adrenocortical carcinoma is a rare and aggressive neoplasm; the clinical presentation is variable. Systemic therapy is important even in patients with localized disease and independent of surgical approach.

Keywords: Adrenocortical carcinoma. Weiss score. Adrenal.

Resumen

El carcinoma corticoadrenal es una neoplasia rara, altamente agresiva, de distribución bimodal, con predominio en el sexo femenino, de la cual el 20% de los casos se diagnostican de manera incidental. Se presenta el caso de un varón de 43 años con dolor de tipo cólico en el flanco izquierdo, pérdida de peso y fiebre intermitente. La tomografía computarizada mostró un tumor en la glándula suprarrenal izquierda y metástasis hepática. Se realizó adrenalectomía radical en bloque, con reporte anatomopatológico de carcinoma corticoadrenal, Weiss de 7 puntos y Ki67 40%. El carcinoma corticoadrenal es una neoplasia agresiva y de presentación clínica variable. La terapia sistémica es importante incluso en pacientes con enfermedad localizada e independientemente de la cirugía.

Palabras clave: Carcinoma corticoadrenal. Puntaje Weiss. Suprarrenal.

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Introduction

Adrenal tumors are common and they affect 3-10% of the population^{1,2}. Between 1-4% of cases presented as incidentalomas, and the majority (up to 80%) as adenomas; only 8% of cases presented as carcinomas².

Corticoadrenal carcinoma (CCA) is a very rare and aggressive condition, with an estimated incidence of 0.5-2 cases per million people/year, and a global prevalence of 4-12 cases per million people/year³. It has a bimodal distribution, with a first peak in children younger than 10, and a second peak during the fourth and fifth decades of life, with a slight prevalence in women, which represent up to 60% of cases¹.

The metastatic disease will be present at the beginning of the diagnosis in 50% of patients, and the other 50% will present progression or recurrence in the short term. The common metastasis locations are primarily the liver and lungs, and less frequently the bones and the peritoneum. There are no absolute malignant criteria for injuries confined to the adrenal gland, but the histological characteristics and a Weiss score ≥ 3 general indicate a malignant condition, as well as the Ki-67 proliferation index $> 20\%$ ⁴.

Clinical case

43-year-old male with type 2 diabetes *mellitus* under adequate control- In the beginning he had colic pain in the left hypochondrium which radiated to the lumbar region of the same side, with a visual analog scale score of 8/10, intermittent fever and unintended weight loss of 10 kg in 3 months. A contrasted abdomen tomography showed a tumor dependent on the left adrenal gland of 10 x 12cm, 91 Hounsfield units (UH) and enhanced to 167 UH after application of a means of contrast, which displaced the adjacent structures, as well as liver injuries in segments VII and VIII with enhancement after applying the means of contrast (Fig. 1). Plasmatic and urinary catecholamines and metanephrines were normal. A radical block adrenalectomy was performed (Fig. 2) without transoperative complications, with bleeding quantified in 1300 ml, adequate postoperative evolution and discharge after four days. The histopathological report was a high level corticoadrenal carcinoma, of 16 cm in diameter, with extensive necrosis (70%) which invades the capsule, with presence of focal lymphovascular invasion, neoplasia free surgical margins, without invasion of adjacent structures and mitotic index of 25 (Fig. 3). In the immunohistochemistry, inhibin, Melan-A and Ki-67



Figure 1. Contrast computerized tomography. **A:** crown section that shows a left adrenal tumor of 10 x 12 cm, 91 UH, with enhancement to 167 UH. **B-C:** axial section showing a left adrenal tumor with displacement of the kidney and the spleen.

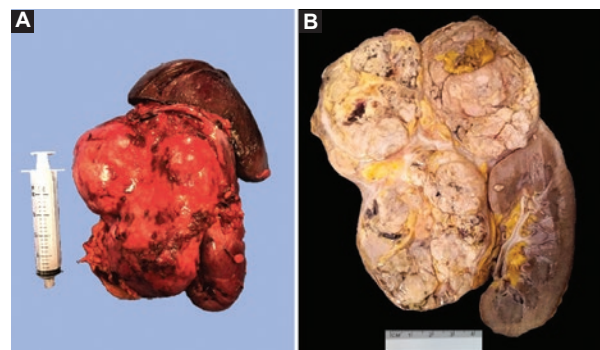


Figure 2. **A:** block resection surgical piece due to tumoral activity. **B:** macroscopic appearance: large, solid tumor with extensive necrosis areas compressing the upper renal pole.

(40%) were positive; chromogranin, synaptophysin and S100 were negative (Fig. 4). The patient is currently in protocol to begin systemic therapy.

Discussion

Adrenal tumors are usually benign, mainly adenomas, in up to 80% of cases¹. Malignant tumors are very rare, and CCA is of primary importance due to its aggressiveness, as survival depends on the stage at the time of diagnosis, with a survival rate of 60-80% after 5 years on stages I and II, a survival rate of 35-50% after 5 years on stage III or locally advanced, and a survival rate of 13% on stage IV^{3,4}.

CCA can be functional tumors in 40-60% of cases⁵, and can produce different clinical syndromes according to the involved hormonal overproduction⁵. Thus, cortisol

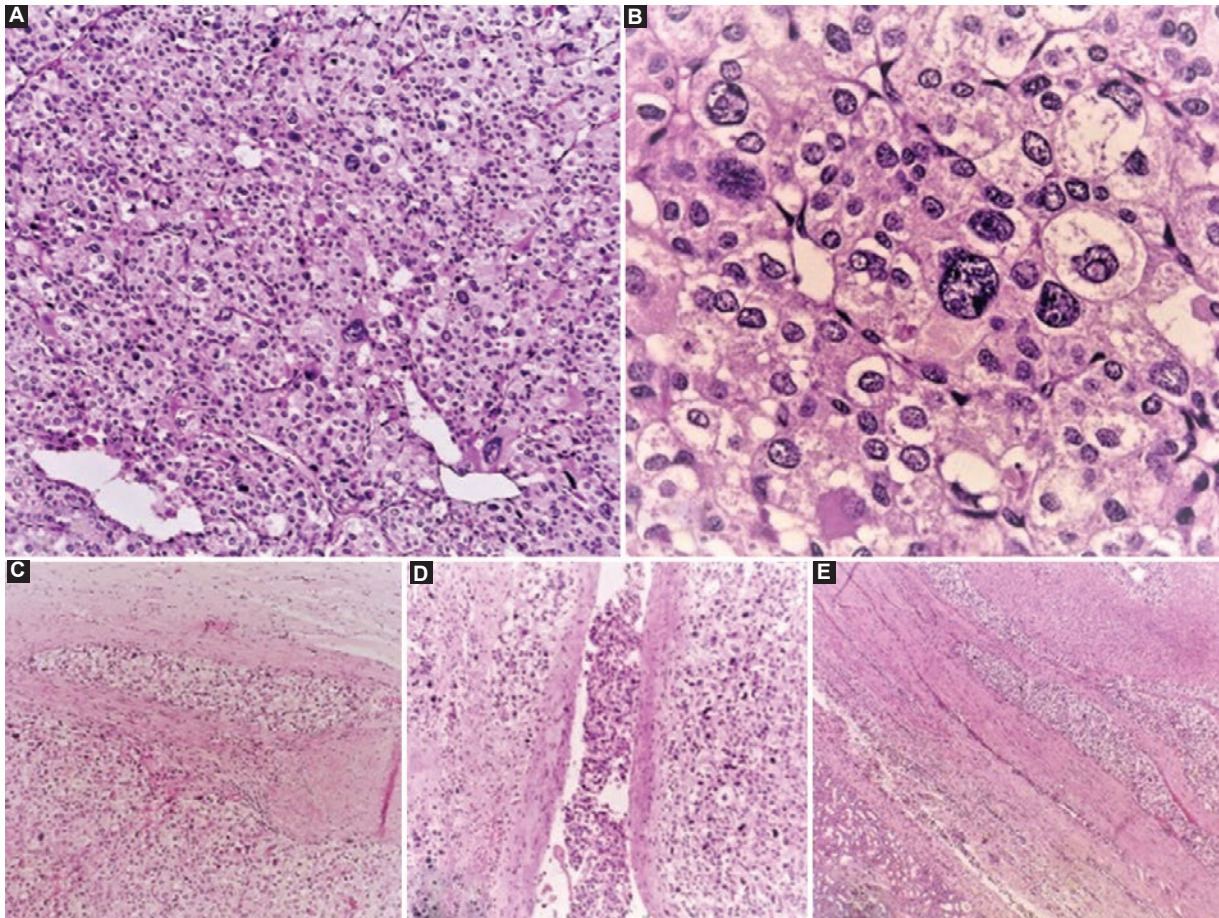


Figure 3. Corticoadrenal carcinoma. **A:** solid growth pattern with cellular heterogeneity. **B:** with higher increase nucleomegalia, coarse granular chromatic can be seen with an irregular distribution and intranuclear inclusions. **C:** adrenal capsule invasion. **D:** vascular invasion. **E:** tumor and underlying kidney without invasion (haematoxylin and eosin staining).

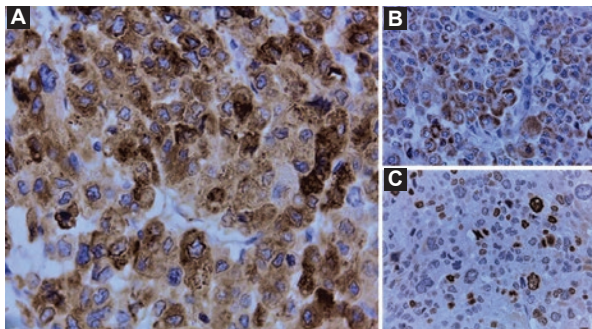


Figure 4. Corticoadrenal carcinoma immunohistochemistry. **A:** positive inhibin **B:** positive Melan-A. **C:** cell proliferation index (Ki-67), 40% nuclear.

levels can be elevated (Cushing syndrome) in 50-70%, androgen elevated (virilization) by 20-30%, estrogen elevated (feminization) by 5%, and mineralocorticoids by 2-3%. In approximately 30-40% of cases symptoms are due to the size of the tumor, which creates a mass effect

on the adjacent organs causing abdominal pain and distension, fullness sensation, nausea, or vomiting. The majority of CCA cases are sporadic, but some have also been associated with hereditary disorders, such as Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Lynch syndrome and multiple endocrine neoplasia type 1, and familial adenomatous polyposis⁶.

During the diagnostic approach, a metabolic panel must be performed including mineralocorticoids, androgens, and catecholamines, which will allow to differentiate between a CCA and other tumors, such as pheochromocytoma; in CCA androgen and cortisol levels rise generally. In a study performed by Sada, et al.⁷, 52.6% were functional tumors, and 47.1% of them were accompanied by cortisol overproduction, 25.1% had combined hormones, 19.3% with sex hormones, and 7.9% aldosterone; the fact that the clinical advanced (IV) as the only independent factor for functional tumors was statistically significant ($p = 0.001$), with 41.4%, versus 21.4% for non-functional tumors.

In the diagnostic approach imaging studies play an important role, as they provide information that can point towards the behavior of malignant tumors, and therefore, it must be noted that CCAs usually present as unilateral tumors of > 6 cm in size in 90% of cases⁵ and with necrotic. In the computerized tomography they are characterized for being tumors with a density of > 10 UH, with a sensitivity of 93-100% and a specificity of 71-72%^{2,6,8} with slow contrast wash (< 50%)⁸; it can also have calcifications and in occasions a thrombus on the renal vein or vena cava. In the magnetic resonance with gadolinium, hyperintense injuries are observed on T2 compared to the liver, and heterogeneous^{8,9}. The 18-F fluorodeoxyglucose-positron emission tomography (18-FDG) may be useful when monitoring patients or when identifying injuries remotely, but it has limited specificity due to the absorption of 18-FDG by the benign adrenal and the pheochromocytomas. Currently, the use of 11C-metomidate as a marker is promising as it can differentiate between adenomas and CCA, and it would be more useful to study of adrenal tumors; however, more studies are needed to prove this¹⁰.

There are certain prognosis factors that can predict patient survival, such as the proliferation index Ki-67 > 20% and Weiss score (nuclear degree, high frequency field mitosis index, atypical mitotic figures, clear cells < 25%, tumor diffuse architecture > 33%, necrosis, vascular invasion, sinusoidal invasion, capsular invasion) > 6, associated with a poor prognosis¹¹⁻¹³. The most important survival predictors in these patients are tumoral degree, tumoral stage and surgical resection¹³.

Immunohistochemistry plays an important role in histopathological diagnosis to determine the adrenocortical origin. There are different biomarkers that can provide the diagnosis, and therefore, it is important to understand specificity and sensitivity of each of them. The steroidogenic factor 1 is considered the most reliable and specific factor, as it is manifested in the non-tumoral adrenal cortex and cortical neoplasias, which is distinctive of steroidogenic tissues; it has a specificity of 100% and a sensitivity of 98-100%¹⁴. Melan-A has been described in steroidogenic tissues with a sensitivity and specificity higher 95%. There are other biomarkers, such as alpha inhibin, calretinin, and D2-40, which can be expressed in adrenal and mesothelial cell tumors. Ki-67, as mentioned above, has prognostic value for diagnosis and survival. Chromogranin-A is usually negative in the CCA and positive in pheochromocytoma.

The classification of the European Network for the Study of Adrenal Tumors (ENSAT)^{6,13}, a stage system that, as with the guidelines of the National Comprehensive Cancer Network (NCCN), indicated that, in stages I and II they are localized tumors of ≤ 5 > 5 cm in size, respectively; stage III is defined by the presence of positive lymph nodes, infiltration of the surrounding tissue or tumoral thrombus in the vena cava or renal vein; and, finally, stage IV corresponds to distant metastasis.

Currently, the only remedial approach for CCA is a complete tumoral resection³, and therefore, even in the metastatic condition it continues to be a therapeutic option to improve survival when complete resection is possible. Adjuvant therapies have the purpose of decreasing the possibility of recurrence⁴. It is worth mentioning that the use of adjuvant therapies is important even when the condition is localized.

Mitotane is an adrenocytolytic drug approved by the FDA and the European Medicines Agency for treatment of CCA. Plasmatic concentrations of > 14 mg/l¹⁵ are required, and the side effects make it difficult to handle due to their toxicity. Other treatment schemes have been studied, but the mitotane approach has not been replaced.

A retrospective study with 177 patients conducted by Terzolo, et al.¹⁶, in which 47 patients received adjuvant therapy and were compared to 55 and 130 (55 group 1 and 75 group 2) without adjuvant therapy, suggest that the use of mitotane after a radical resection of the CCA significantly prolongs survival free of recurrence after 42, versus 10 months in the control group 1, and 25 months in control group 2.

The FIRM-ACT trial, conducted by Fassnacht, et al.¹⁷, included 304 patients with metastatic CCA and compared to the association of mitotane with etoposide, cisplatin, and doxorubicin (M-EDP) in contrast with mitotane and streptozotocin (M-Sz) as first or second line treatment, obtaining higher survival rates free of progression with M-EDP: 5.0 months compared to 2.1 months with M-Sz ($p < 0.001$).

In our patient, without clinical or biochemical functionality evidence, who started with a clinical stage IV advanced disease with metastatic liver activity, a block resection was necessary, obtaining negative margins in the surgical piece. Even so, a systemic adjuvant therapy is necessary. However, the prognosis is poor due to the Weiss score of 7 points, the Ki-67 of 40%, and clinical stage IV, and therefore, the survival chances of 5 years will be less than 13%.

Conclusions

CCA is a very rare and aggressive neoplasia with a variable clinical presentation. Even though it is diagnosed incidentally, in the majority of cases it presents as an advanced disease at the time of diagnosis. For the histopathological study, it is important to perform immunohistochemistry and proliferation and mitotic index, as they help establish the prognosis and differentiate neuroendocrine tumors other than CCA. Surgical resection continues to be the standard treatment with highest survival rates, and adjuvant therapy with mitotane, even in patients without metastasis, is a therapeutic option that improves survival.

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Conflicts of interest

The authors state that they do not have any conflicts of interest.

Ethical disclosures

Protection of People and Animals. The authors state that no experiments have been conducted in humans or animals for this research.

Data Confidentiality. The authors state that the protocols of their work center regarding the publication of patient data have been followed.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects mentioned in the article. This document is owned by the corresponding author.

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