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CASE REPORT

Adrenocortical carcinoma: A tumor with poor answer to classic chemotherapy

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Introduction: Adrenocortical carcinoma (ACC) represents a rare endocrine malignancy being the second most aggressive endocrine cancer after anaplastic thyroid cancer. [1]. While most of them arise sporadically, up to 15% of adult ACC patients are related to germline mutations associated with familial cancer syndromes.[1,2]. Current treatment strategies include surgery as well as systemic therapy with mitotane and chemotherapy. **Case report**: A 60-year-old female patient with a family history of colon cancer, multinodular goiter, hypothyroidism treated with substitutive therapy, uterine fibroids, and hypertension, was diagnosed with adrenocortical carcinoma. No distant metastasis were present at the moment of diagnosis so an adrenalectomy was performed. Due to postoperative complications, a total nephrectomy was also needed. Adjuvant Mitotane treatment was given. A CT exam performed 5 months after the resection showed multiple pulmonary metastasis, a liver nodule and peritoneal carcinomatosis. The standard first-line chemotherapy of choice was Carboplatin and Etoposide. After completing 3 cycles of chemotherapy the imaging reassessment show the progression of liver and peritoneal lesions and the quasi-complete regression of lung lesions. Currently, the Mitotate treatment was stopped due to severe adverse reactions. **Conclusions**: Adrenocortical carcinoma is a rare endocrine malignancy with a poor prognosis. The recruitment of ACC patients for new clinical trials to investigate new treatment strategies is needed because currently, no significant therapeutic breakthrough is emerging.

Keywords: adrenocortical carcinoma, Weiss score, familial cancer syndromes, Mitotane

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Introduction

Primary malignancies involving the adrenal glands are exceedingly rare, adrenocortical carcinoma (ACC) having an incidence of 1 to 2 per million people annually [1,2,3]. A slight prediction for women was noted (female to male radio 1.5:1) as well as a bimodal age distribution, regarding patients in early childhood and those in the fifth decade of life [1,2,4]. The poor prognosis of this disease is due to the advanced stage at diagnosis. About 40% of cases are detected when the metastasis are already present, with overal lsurvival (OS) at 5 years of 20-25% [4,5,6].

Up to 15% of adult ACC have germline mutations but most ACC occur sporadically.[1,2,3]. Familial cancer syndromes involving ACC are Li-Fraumeni syndrome (LFS), Lynch syndrome, multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis (FAP), Beckwith Wiedemann syndrome, and Carney complex [1,2,3]. In adults, somatic mutations of the *TP53* gene are observed in more than 50% of cases and are correlated with a more aggressive phenotype [4]. Only a few case reports can be found in the Medline database regarding the association of ACC with Lynch syndrome. The incidence of association is estimated at 3.2% [5]. The majority of patients present with functional cortical neoplasm associated with hypercortisolism and hyperandrogenism [2,6].

When a clinical suspicion is encountered, the diagnosis of adrenal tumors relies on hormonal workup and imaging assessment [2]. The pathologic evaluation is required to make a definitive diagnosis of ACC, Weiss criteria being by far the most widely used scoring system [1,7,8].

In the management of ACC, a multidisciplinary team is needed [1]. The treatment involves the surgical resection of the primary tumor, the keystone of ACC treatment, the use of Mitotane in an adjuvant setting, and the combination of Mitotane and chemotherapy for the unresecable or metastatic disease [1,3]. In this paper, we present a case of ACC, in a patient with a family history of colon cancer, and a review of literature. The signed informed consent of the patient was obtained for therapy and publication of the scientific data.

Case report

A 60 years old female patient presented in the Oncology clinic with a personal history of multinodular goiter, hypothyroidism treated with substitutive therapy, uterine fibroids, for wich a total hysterectomy with bilateral salpingo-oophorectomy was performed, and hypertension. The patient family history shows that both parents, two brothers, and also a cousin have all been diagnosed and

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treated with colon cancer. There were no specific symptoms at presentation.

Investigation and surgical treatment

The patient related that, before presentation in the Oncology Clinic, a CT exam showed a heterogeneous tumor of the right adrenal gland with a diameter of 123/120/150 mm, without a cleavage plane on the right liver lobe and the right kidney. Few bilateral pulmonary nodules up to 8 mm in size indicated the suspicion of secondary determinations. The treatment of choice was a radical resection of the tumor, respectively right adrenalectomy. As, postoperatively, the patient presents significant bloody secretions on the drain tube, relaparotomy and right nephrectomy were carried out.

Histopathology

On the gross description, the fragmented tumor has an orange-brown color, with whitish areas, an extremely friable consistency, and presented extensive areas of necrosis and hemorrhages. The size of the tumor fragments exceeds 5 cm and the total weight was about 950 g. One of the tumor fragments was covered by a smooth capsule which was crossed by the the tumor tissue.

Under the microscope, solid tumor proliferation with a diffuse architecture was described. The large tumor cellsshowed a predominantly oxyphil aspect with fine granular cytoplasm. Highly pleomorphic nuclei with obviously seen nucleoli were also seen. The mitotic rate was of 10 mitoses/50 fields, at ob 40x (high-power fields). Infiltration and rupture of the capsule were noted. Extensive areas of necrosis were evident. The Weiss score was estimated to be of 7 and the tumor was staged as pT3 (Figure 1).

Laboratory and imagistic investigations

A PET CT investigation was requested, considering the suspicious lung lesions highlighted in the previous CT examination. As the pulmonary nodules display reduced FDG uptake, the suspicion was not confirmed.

Laboratory assessment at diagnosis: free cortisol 12.8 ug/dL (3.7-19.4 ug/dL), cortisol after dexamethasone suppression test 4.7 ug/dL, DHEA sulfate 2375.3 ug/dL (25.9-460.2 ug/dL), testosterone 410.76 ng/dL (10.83-56.94 ng/dL), Potassium 5 mEq/L (3.5 to 5.5 mEq/L).

Postoperative chemotherapy and follow-up

Mitotane treatment was postoperatively started with a dose of 2 g/day. The increase in dose was done till the serum concentration of the drug was reached 14-20 mg/L.

Three months after the PET CT examination another CT was performed. It revealed systemic spread and multiple metastasis, respectively 7 pulmonary nodules (12 mm), a liver nodule in the 5th segment (27/28 mm) and peritoneal carcinomatosis.

For the metastatic ACC, the preferred regimen was decided to be Carboplatin+Etoposide+Mitotane.

After completing three cycles of chemotherapy, the imaging reassessment showed the progression of liver and peritoneal lesions and the quasi-complete regression of lung lesions. Mitotane treatment was stopped due to severe adverse reactions. They consisted of gastrointestinal disorders like diarrhea andvomiting as well as central vestibular syndrome including vertigo and postural instability.

Currently, the patient is in the evidence of another hospital and is under chemotherapy treatment.

Discussions

ACC is an aggressive and rare malignancy, and at the time of diagnosis metastasis are commonly present [6,7,8]. Currently, using radiologic investigations, an increasing discovery of incidental adrenal masses can be seen. Therefore, the differential diagnosis between benign and malignant tumors is a difficult task for imagisticians [7].

Usually, patients with ACC present symptoms related on the hormonal overproduction [1,3,9]. Hormonal workup reveals in 50-80% of hormonal-secreting ACCs hypercortisolism, which can lead to hypokalemia and hypertension. The second most commonly synthesized hormones,in 40-60% of the cases, are adrenal androgens, which can cause virilization in women. By contrast, aldosterone secretion is relatively rare in ACC [1,9].

Previous studies have shown us that 92% of ACC are larger than 6 cm at diagnosis [1,3]. The most useful imaging method of investigation is CT-scan, with 100% sensitivity and 68% specificity [1]. PET-CT is mostly used to assess the response to chemotherapy [3].

European Network for the Study of Adrenal Tumors (ENSAT) staging is currently used for ACC staging [3,9]. The staging system proposed by ENSAT has been adopted

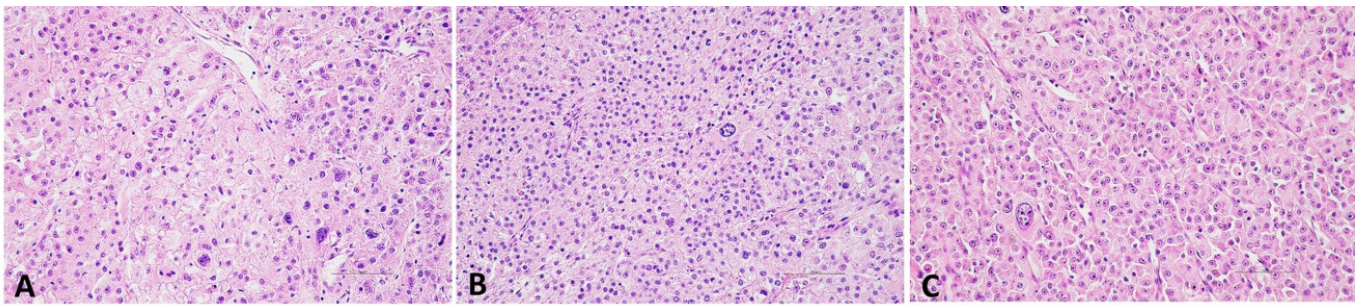

Fig. 1 Histological aspect of the adrenocortical carcinoma: A. Well-vascularized tumor with clear cells and pleomorphic nuclei; B. Eosinophilic cytoplasm and small nuclei; C. Well-visible nucleoli. Ob. 20x

by the American Joint Committee on Cancer (AJCC) in its eighth edition [2].

It is discouraged the diagnosis of ACC through fine needle aspiration (FNA) due to the high false-negative rate. Moreover, complications may occur in 11% of patients. This is the reason why the diagnosis is usually done through pathologic evaluation of the surgical specimen [1,10].

Macroscopically, ACCs tend to be large lobulated masses confined by a fibrous capsule, with heterogenous areas of hemorrhage and necrosis. Depending on the intracellular lipid content they appear from brown to orange or sometimes yellow [10].

Microscopically, the Weiss scoring system,is the most widely used [1,10]. It includes nine histologic features that are assessed at light microscopy. The presence of three or more correlates with malignancy [1,7,8,10]. These features include: high nuclear grade (III or IV), a mitotic rate higher than 5 per 50 high-power fields (HPFs), presence of atypical mitoses, clear lipid-rich cells representing less than 25% of the tumor, >33% diffuse architecture, necrosis, venous invasion, invasion of sinusoidal structures, and invasion of the capsule [7,8,10,11].

While most cases of ACC are sporadic, a minority of cases might be associated with other syndromes [11]. Depending on their prevalence they are listed as common (LFS and LS), rare (MEN 1, FAP and Beckwith-Wiedemann) and very rare associations/case reports (NF1, Carney Complex and Birt-Hogg-Dube) [12].

The main oncogene involved in ACC genesis is the insulin-like growth factor 2 (IGF-2) but the molecular mechanism is not yet fully understood [1,11].

Due to the fact that our patient didn't receive any genetic testing, we cannot know if a genetic syndrome was associated. A genetic family consult was recommended for the suspicion of LS or FAP.

As regards therapy, surgical resection remains the keystone of ACC treatment.The use of Mitotane, an adrenolytic drug, in an adjuvant setting/advanced disease might prolong the relapse-free survival (49-55% in patients treated with Mitotane *vs*. 70-90% in control groups) [1,11,13]. First-line systemic therapy consists of Carboplatin/Cisplatin, Doxorubicin, Etoposide, and Mitotane [11]. Pembrolizumab, a humanized monoclonal antibody that targets the programmed cell death ligand, has shown to be efficient in tumors with microsatellite instability-high and/or mismatch repair deficiency (MSI-H/MMR-D) [11]. Negative prognosis factors for ACC are cortisol production, tumor stage and tumor grade [14].

Conclusion

ACC remains a highly aggressive endocrine malignancy for which classic chemotherapy is far from having good results. As it is rarely encountered in daily practice, familial genetic advice is rarely recommended. In any patient with ACC, however, association with inherited cancer predisposition syndromes should be checked.

Authors' contribution

SAD (writing – original draft, visualization, clinical followup, resources and formal analysis);
STB (data curation, analysis, and literature review);
TC (investigation, validation and oncologic therapy);
VA (investigation, data curation and oncologic therapy);
GS (interpretation of the differential diagnosis, writing – review and editing, funding acquisition, supervision);

Conflict of interest

The authors declare no conflict of interest.

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