Adrenocortical carcinoma - a diagnostic and therapeutic challenge

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Abstract

Carcinoma of the suprarenal cortex is a rare and aggressive neoplasm, associated with a negative prognosis. Its pathogenesis is not yet fully understood. Most of these tumors appear to be sporadic, but some associated hereditary syndromes have been described. There are no specific aspects that characterize malignant neoplasm. The heterogeneity of the clinical, laboratory, imaging and pathological findings make this diagnosis a challenge, even for an experienced multidisciplinary team. Surgery remains the chance of cure, when a complete resection is possible. There is currently no medical treatment that has shown convincing results for advanced disease. Progress can be expected in the future, thanks to a better understanding of the molecular mechanisms of tumorigenesis of suprarenal tumors. The authors review the epidemiology, pathogenesis, diagnosis, treatment and prognosis of this disease, illustrating with two separate clinical cases.

Key words: adrenocortical carcinoma, mitotane, chemotherapy.

INTRODUCTION

Carcinoma of the suprarenal cortex is a rare and aggressive malignant neoplasm, associated with a bad prognosis.

Most cases seem to be sporadic, however, it has also been described as a component of some hereditary syndromes.

Imaging, through CT or MRI, usually shows a heterogeneous voluminous mass, with a small fat content.[1]

Complete surgical resection (R0) is the only treatment that can potentially cure it, and the only one that enables long term survival, therefore it is the first treatment of choice in stages I through III (limited, localized disease). However, even after complete excision, most patients will have local recurrence or distant metastasis.

For patients who cannot undergo surgery, mitotane (in isolation or associated to cytotoxics) remains the treatment of choice.

Despite the treatment options available, the overall five-year survival rate is less than 30% for most series.[1]

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EPIDEMIOLOGY

This rare, but highly malignant type of neoplasm has an incidence rate of one to two per million per year, and accounts for approximately 0.2% of deaths due to cancer.[2,3]

This rate of occurrence has a bimodal distribution, with a first peak in infancy and a second, more prominent one in the fourth or fifth decades of life. An exception to this distribution is found in South of Brazil, where the annual rate of occurrence of adrenocortical carcinoma is abnormally high for children under 15 years of age. This disparity seems to be related to a localized mutation on gene p53 that is prevalent in the region, and is apparently related to environmental factors.[2,3]

It appears to be more common among females (1.6:1) and for these cases, the tumors are mostly functioning.[1,4]

PATHOGENESIS

The molecular pathogenesis of this neoplasm is still not fully understood, particularly where it evolves from benign adenomas.[5]

Most cases of adrenocortical carcinoma seem to be sporadic, but some associated hereditary syndromes have been described. The first to be described (Sameshina *et al.*, 1992) was Li-Fraumeni syndrome, with which this neoplasm is associated in 1% of cases.[2,3] For these patients, a germinal mutation was found in tumor suppressor gene p53, located in the 17p13 locus. In this tumor, the second allele of the

gene appears to be inactivated by a second somatic mutation, resulting in complete loss of gene activity. For the infant population in the South of Brazil, mentioned above as most affected with adrenocortical carcinoma (ten times more than the rest of the world), the affected gene is also p53. In this case, a localized germinal mutation in the gene seems to have a tissue specific effect, i.e. it is associated with this tumor location only.

Another associated hereditary syndrome described is Beckwith-Weidman Syndrome, also related to Wilm's tumor, neuroblastoma, and hepatoblastoma. Mapped in locus 11p15, it is related to the overexpression of IGFII (Insulin-like growth factor). IGFII overexpression was also demonstrated by Giordano et al., in 2003, in 90% of cases of sporadic adrenocortical carcinoma, through the use of microarray analysis. [3]

Other hereditary cancer syndromes that may also include adrenocortical carcinoma are MEN-1 (Multiple Endocrine Neoplasia Type 1), with which are associated pituitary gland tumors, parathyroid and pancreatic neuroendocrine tumors, and which are the result of mutations that inactivate the MEN1 gene, at chromosome 11q, and SBLA syndrome (sarcoma, breast, lung and adrenal).[4]

CLINICAL PRACTICE

The clinical practice for this pathology is very heterogeneous, this is partly due to the fact that these tumors may be secreting or not, and partially because of those that are secreting, the dominant hormone type determines the type of presentation.

Secreting or functioning tumors (about 60%) mostly present signs and symptoms resulting from the excess hormone produced by them. Thus we find, among the more frequent syndromes, Cushing syndrome, virilization syndrome, feminization syndrome, and mixed Cushing-virilization syndrome.[6]

Cushing syndrome, whether associated or not with virilisation, is the most frequent condition. Central obesity, muscle weakness, skin atrophy with skin striae, hyperglycemia, hypertension, and psychiatric symptoms are the most frequent symptoms/signs.

Excess androgens in women causes hirsutism, androgenic alopecia, voice changes, mammary atrophy and menstrual changes, often associated with infertility. In men, on the other hand, the hypersecretion of estrogen manifests through gynaecomastia and testicular atrophy.

Hypersecretion of aldosterone in suprarenal cortex carcinomas is rare, and is revealed through hypokalaemia and hypertension.

Hypertension can therefore be related either to excess glucocorticoid or mineralocorticoid, or to the simple activation of the renin-angiotensin system by renal vascular compression, induced by the tumor mass.[6]

Tumors are considered non-functioning when they do not produce hormones in excess, or hormone precursors and/or active hormones in sufficient quantities to have clinical consequences. These tumors are diagnosed later, and manifest themselves with symptoms related to their growth and consequent local mass effect: feeling of abdominal fullness, gastrointestinal symptoms, nausea, vomiting and, sometimes, pain.

In a minority of cases, there are only constitutional symptoms, such as asthenia, anorexia and sub-fever temperatures. Even in the presence of large tumor masses, the inflammatory response unleashed is not very strong.

It should be noted that the clinical diagnosis of a patient with a carcinoma of the suprarenal cortex is not static, but and may change during its evolution; quantitative and/or qualitative changes in hormone secretion can transform an initially nonfunctioning tumor into a functioning tumor.

DIAGNOSIS

The suspicion of carcinoma of the adrenal cortex is initially raised by a combination of clinical, biochemical and imaging criteria and finally confirmed by histopathology.[2]

Distinguishing an adrenocortical carcinoma from a benign adenoma is a challenge because there are clinical and pathological areas of overlap between these two entities.[7]

The percentage of functioning or secreting tumors varies between 25% and 80% among the various series reported in the literature.[1] In such cases, the metabolic syndrome they unleash, guides the diagnosis. The remainder (non-secreting) are silent and, in most cases, unless they appear as incidental findings on imaging studies or during surgery carried out for other causes, they are diagnosed only when they reach large dimensions, producing symptoms due to the compression of structures, or spreading from their original site.

Currently, the diagnosis of adrenocortical carcinoma is most frequently made through an "incidentaloma" study.

Hormone research

The diagnosis of excess steroids is useful for establishing the adrenocortical origin of the tumor, and can be used for follow-up.

Increased cortisol secretion, independent of ACTH (adrenocorticotrophic hormone) is easily demonstrated by the increased excretion of cortisol in the urine – which is not suppressed by high doses of dexamethasone – and undetectable levels of ACTH.

At the same time, also in response to dexamethasone, increased levels of 17-hydroxyprogesterone are seen, and also of dehydroepiandrostenedione sulfate (DHEA-S) leading to increased levels of testosterone in women.

Other steroids that may be elevated are desoxycortisone, delta 4-androstenedione and estrogens.

Aldosterone secretion by this type of tumor is uncommon, but can be detected by a simple measurement of aldosterone and renin. Some recommend its study it in patients with hypertension and/or hypokalaemia, suggesting an excess of mineralocorticoids.

All this hormone study can test negative if it is a non-secretor tumor, which accounts for about one third of the cases.

Measuring the plasma metanephrines and/or urinary catecholamines in 24-hour urine is also recommended in the initial diagnosis of suprarenal tumors, to eliminate phaeochromocytomas.

TABLE I

Hormone research on patients with adrenocortical carcinoma

Glucocorticoid secretion
Basal ACTH
Basal Cortisol
Dexamethasone suppression test
Urinary free cortisol and urinary creatinine (24h urine)
Sex steroids
Testosterone (in women)
Estradiol (in men and post-menopausal women)
Androstenedione
Dehydroepiandrosterone-sulfate (DHEA-S)
Precursors
17-OH-progesterone
Deoxycorticosterone
Mineralocorticoids
Aldosterone
Renin

Diagnostic imaging

Diagnostic imaging has a critical role, not only in the detection and characterization of suprarenal masses, but also for their staging, through the detection of local and/or distant invasion.

CT is an informative test for this type of injury, and it is usually the test of first choice. Most adrenocortical carcinomas appear in the form of a unilateral voluminous mass (usually over 10 cm), located in the upper pole of the kidney.

The findings that are more suggestive of a malignant tumor, besides the size of the tumor (< 3 cm most likely benign and > 5 cm most likely malignant), are irregularities in the borders and heterogeneity, with foci if necrosis. Another, more specific aspect and, which has better power to distinguish, has to do with dynamic aspects of contrast acquisition.[1,8]

There is no evidence to suggest that MRI is better than CT, except in the evaluation of vascular invasion. The sensitivity, specificity, and positive and negative predictive values of both tests are about 90%.[3] However, when the results of the CT are ambiguous, the next recommended test is MRI.[8]

Adrenal scintigraphy with NP-59 (^{131}I-6-iodomethyl-19-norcholesterol), a cholesterol analog that has higher concentrations in the adrenal gland, is a useful test, but is little used because its limited availability, and its usefulness has still not yet been fully demonstrated. In addition, it is a length test (3 to 5 days) and requires high doses of radiation.[5]

In relation to PET with 18F-FDG (18F-2-deoxy-2-fluoro-D-glucose) it appears to distinguish between adenomas and malignant tumors, however, it is not specific to any malignant tumor.[1,4,8] Substitution of 18-fluorodeoxyglucose (FDG), by ^{11}C-metomidate, a 11β hydroxylase inhibitor that is specific to the adrenal tissue, appear to improve the accuracy of the PET examination, with fewer false negatives in these tumors, assuming an important role both in the differential diagnosis of adrenal masses, and in

assessing the extent of the disease and detection of recurrence.[8,9]

Osteoarticular scintigram, during the screening tests for bone metastasis, should only be performed, if there is a clinical suspicion. In the case of secreting tumors, with hypercortisolism, false positive results may occur for this test.

The role of fine needle biopsy

Given the risk of tumor spread through the path of the biopsy needle (about 3%), [8] currently the procedure is only indicated in cases of inoperable disease, before the introduction of chemotherapy or radiotherapy in patients with a history of other malignant neoplasm (especially lung, breast and kidney), with no signs of other metastases, and always after the exclusion of pheochromocytoma.[3,9]

TABLE II

Weiss Histological Criteria

Histological Criteria	Semi-quantitative criteria	Score
High nuclear grade	Present or absent	0 or 1
High mitotic level	> 5/50 field large amplitude	0 or 1
Atypical mitosis	Present or absent	0 or 1
Low % of clear cells	< 25% of tumor cells	0 or 1
Foci of necrosis	Present or absent	0 or 1
Diffuse architecture standard	> 33% of tumor	0 or 1
Venous Invasion	Present or absent	0 or 1
Sinusoid Invasion	Present or absent	0 or 1
Capsular Invasion	Present or absent	0 or 1
One score≥3 indicates malignancy.		

Histopathology

Even in histopathology terms, the diagnosis of malignancy in this location is not straightforward and there is no single pathological finding that is sufficient to make this diagnosis, which makes this diagnosis a challenge, even for an experienced anatomopathologist.

The study of tumors that show local invasion or metastasis, and are therefore obviously malignant, enabled the creation of some classification systems that combine a number of criteria in order to establish a score. The most widespread is that proposed by Weiss et al. [10]

This classification system includes nine histological criteria: high nuclear grade, high mitotic rate, presence of atypical mitosis, low percentage of clear cells (<25%), diffuse architecture, necrosis, permeation of venous structures, invasion of sinusoids, and capsular invasion.[6, 9] (*Table II*). A score above 3 is indicative of malignancy.

Although they provide a guideline, these systems have certain limitations, given their high dependence on the pathologist's experience.[9]

Immunohistochemical findings

Adrenocortical carcinomas are usually negative for cytokeratins (CK7 and CK20), and positive for vimentin, Melan-A and inhibin α.

The Ki-67 proliferative index can also be useful in this distinction, although some of these malignancies may present a low index. Non-functioning or non-secreting tumors seem to present a higher Ki-67.[8]

The overexpression of IGF-2, cyclin E can also guide this diagnosis, as well as the β-catenin immunofixation standard.[5]

Molecular markers

The limitations of the classical histopathologic approach have led to research on other predictors of malignancy.

Some molecular markers have been studied in combination with the malignancy of these tumors, namely the overexpression of IGF-II, uniparental disomy of 11p15, loss of heterozygosity for 17p13 and overexpression of topoisomerase 2A.

Its routine use is not recommended as yet.[9]

STAGING

The staging system for these tumors initially proposed by MacFarlane, and further modified by Sullivan et al, is currently the one with highest consensus. [11]

Patients in stages I and II have tumors confined to the suprarenal gland, with varying dimensions (< 5 cm, in stage I and ≥5 cm, in stage II). In stage III, local invasion is observed (extraglandular) but without reaching the adjacent organs or regional lymphatic ganglions. Finally, in stage IV, there is distant metastasis and/or invasion of adjacent organs and/or regional ganglions *(Table III)*.

The main locations of distant metastasis are, in

TABLE III

McFARLANE Staging

Stage I	Confined to the gland, ≤5cm
Stage II	Confined to the gland, >5cm
Stage III	Any mobile node of any size or local invasion (no invasion of neighboring organs)
Stage IV	Invasion of adjacent organs or fixed nodes and/or distant metastasis

descending order of frequency, the liver, the lungs and the bones.

Unfortunately, according to the general literature, by the time they are diagnosed, most tumors are in stage IV, with the exception of the subgroup children aged under 10 years, where the disease is diagnosed in earlier stages.[6]

Currently, TNM staging, which is practically superimposable on the McFarlane staging, is also used.

PROGNOSTIC FACTORS

The correlation between clinical manifestations and survival has been widely researched: most authors report that prognosis is not related to tumor functionality, however, Karakousis et al., and Hogan et al., suggest that functioning tumors may have a better prognosis.[6]

The stage has proven to be one of the most important factors of prognosis. Although no significant differences in survival rates were found between stages I and II, survival is drastically reduced for stage IV, while stage III presents an intermediate value. [6]

The extent of the surgery, i.e. the possibility of a complete resection, is also one of the most important factors of prognosis. After complete surgery, a five-year survival of between 11% and 65% has been registered.[10]

Various studies have shown that factors such as age, Weiss's score, loss of heterozygosity of 17p13 and mitotic index may be independent prognostic factors, related to recurrence-free survival, however, many of these studies do not take into consideration the stage of disease, which can affect the results.[10]

A study published in 2007 (Assié et al) which included only metastasized patients also showed that the number of metastatic sites, mitotic index, and Ki67 may have some prognostic value.[12]

TREATMENT

Surgery

Open adrenalectomy, with complete tumor resection (R0), by an experienced surgeon, is the only approach that enables prolonged remission to be obtained in stages I to III, given the limited options available in terms of effective adjuvant treatment. In-block, total or partial resection of the invaded neighboring organs (kidney, liver, spleen, pancreas and stomach) and regional lymphadenectomy should be performed jointly with the extraction of the venous thrombi from the inferior and renal vena cava, if present.

The benefit of resection of the primary tumor in metastatic disease (stage IV) and an indication of aggressive resection for recurring adrenocortical carcinoma and resectable metastatic disease are still the subject of debate.[1]

In the case of stage IV functioning tumors, cytoreduction surgery, with resection of the primary tumor, has been shown to improve prognosis.[9]

Mitotane

Bergental et al. described, for the first time in 1959, the beneficial effect of o',p'-DDD (ortho, para-dichlorodiphenyldichloroethane) or mitotane, in patients with metastatic carcinoma of the suprarenal cortex.

This drug, an analog of the DDT pesticide, comprises of a potent adrenolytic with specific activity in the suprarenal cortex (Schteingart, 2000). [14]

Of the pharmacological agents described as adrenal function suppressors, mitotane appears to be the only one that inhibits the biosynthesis of steroids and at the same time, destroys the adrenocortical cells (direct cytotoxic effect).[6]

Mitotane is currently marketed in Europe, in an oral formulation, in the form of 500 mg tablets (Lysodren®, Bristol Myers Squibb).

In low doses (≤ 3 g/day) mitotane ensures a suppressant effect on adrenal steroid secretion. In doses over 3 g/day, an adrenolytic effect is observed. In the treatment of patients with adrenocortical carcinoma, doses vary between 6-15 mg per kg of weight, divided into three to four daily doses. Serum levels reach a plateau after 8 weeks of treatment and should be monitored, given the narrow therapeutic window. Therapeutic levels are between 14 and 20 mg/dL.

Monitoring of mitotane therapy, besides including determining serum levels of the drug, also includes measurements of electrolytes, serum ACTH and uri-

nary cortisol.

The side effects of mitotane are generally related to plasma levels of the drug, and rarely show levels below 20 mg / dL. The most common side effects are gastrointestinal (nausea, vomiting, anorexia and diarrhea) and occur in about 80% of patients. Neuropsychiatric symptoms such as lethargy and drowsiness may occur in 25% of patients. Ataxia and changes in speech can occur less often, and are more often associated with toxic levels. Nonspecific rash, genitourinary symptoms and hepatotoxicity may also occur. Analytical changes, such as hypercholesterolaemia, hypertriglyceridaemia and alterations in liver tests are also very common.

In cases of severe toxicity, or side effects that are unbearable for the patient, the treatment may be reduced or discontinued, however, given the affinity of mitotane to the adipose tissue, serum levels only begin to decline after 6 to 8 weeks.

Because the normal adrenal tissue is also a target for the drug, adrenal insufficiency is induced in almost all patients. Hormone replacement therapy (glucocorticoids and mineralocorticoids and, sometimes, levothyroxine) should be started between the second and fourth weeks. The use of lipid-lowering is further recommended, given that the drug is highly lipophilic and tends to bind to lipoproteins at very low densities (LDL and VLDL).[15]

In terms of clinical efficacy, most of the results described in the literature are for retrospective studies, with objective response rates varying between 25% and 35%, the majority being partial and transient.

A recent meta-analysis, published in 2006 by Allolio, analyzing only prospective studies with more than 10 patients, found an average objective response rate of 25%.

In terms of survival, the benefits have not been fully established, however, a study of 202 patients, published by Abiven et al., in 2006, shows an impact on survival in the subgroup of patients with cortisol hypersecretion. [16]

The role of mitotane as an adjuvant after complete surgical resection remains subject to debate, since in some series, it appears to be associated with a worse prognosis.

Chemotherapy

Despite the relative effectiveness of the adrenolytic agent mitotane in the treatment of advanced disease, objective tumor regression is verified in only about 25% of cases.[15]

In non-responding patients, or those whose disease progresses despite the mitotane and those in whom the treatment has to be suspended due to toxicity, the use of other cytotoxic drugs was tested.

Due to the rarity of the disease, cytotoxic treatment with chemotherapy, in carcinoma of the suprarenal cortex, was initially cited in individual cases or small series, and until recently, no more than nine first line phase II trials have included 10 or more patients. For second line trials, the number is, as expected, even smaller.

Several cytotoxic agents have been used, with objective response rates of between 10% and 40%.[17]

Part of this therapeutic refractoriness can be explained by the strong expression of the multidrug resistance type 1 (MDR1) gene that is characteristic of these tumors. One of the most commonly studied and used agents, whether alone or in combination, is cisplatin which, curiously, is not a target of the MDR1 gene.

In light of current knowledge, monochemotherapy does not seem to be the most logical choice of treatment.[15]

Studies with cell lines showed that adrenolytic mitotane partially reverses the mechanism of multidrug resistance mediated by glycoprotein p/MDR-1, which supports the association of this drug with chemotherapy regimens.[15,18]

Of the various protocols tested (*Table IV*) the Italian regime (Berruti et al., 1998) seemed to show the best results, combining etoposide, doxorubicin and cisplatin, with mitotane. [19,20] In a phase II trial with 72 patients, the objective response rate was 49%, including 5 patients with complete response. However, this rate was obtained at a cost of significant toxicity.

In another study (Kahn et al., 2000) the combination of streptozocin with mitotane was also proposed, with an overall response rate of 36%, and with less toxicity. This protocol was also tested in the adjuvant setting, allowing a significantly longer disease-free survival, compared to the control group.[21]

The FIRM-ACT trial, the first randomized, phase III, multicentre trial, which is still underway, was developed with the goal of comparing these two therapy regimens, which are still considered by International Consensus as the best choices for the treatment of carcinoma of the adrenal cortex.[15,18,22]

TABLE IV

Chemotherapy protocols studied

Study	Protocol	Nº of Patients	CR	PR	Objective response rate
Van Slooten *et al.* 1983	Cisplatin Doxorubicin Cyclosphosphamide	11	—	2	18%
Schlumberger *et al.* 1991	Cisplatin Doxorubicin 5-FU	13	1	2	23%
Decker *et al.* 1991	Doxorubicin	16	1	2	19%
Bukowski *et al.* 1993	Cisplatin Mitotane	37	1	10	30%
Burgess *et al.* 1993	Cisplatin Etoposide	13	—	6	46%
Bonacci *et al.* 1998	Cisplatin Etoposide Mitotane	18	3	3	33%
Berrutti *et al.* 1998	Cisplatin Etoposide Doxorubicin Mitotane	28	2	13	54%
Williamson *et al.* 2000	Cisplatin Etoposide	45	—	5	11%
Kahn *et al.* 2002	Streptozocin Mitotane	22	1	7	36,4%
Abraham *et al.* 2002	Vincristine Etoposide Doxorubicin Mitotane	36	1	4	54%

CA- Complete Response; PR- Partial Response; Objective Response – Partial Responses + Complete Responses
Adapted from Bertagna 2006[8]

Trials with drugs such as gemcitabine or taxanes have also been conducted, still with unconvincing results.

Phase II trials are currently underway with an MDR1 pump inhibitor (tariquidar®) and epidermal growth factor receptor inhibitors (Geftinib and Erlotinib), endothelial vascular growth factor inhibitors (Bevacizumab) and tyrosine kinase (Sunitinib and Sorafenib).

Radiotherapy

External radiotherapy in the local treatment of adrenocortical tumors has been considered ineffective.[17]

The use of tumor bed radiotherapy in an adjuvant setting has been studied, taking into account the high rate of local recurrence, even after complete surgeries.

Despite being considered an ineffective treatment for this type of neoplasm, some trials, although involving a small number of patients, appear to show benefíts.[12] A recent German (M Fassnacht, 2006) retrospective trial, involving 14 patients, showed a reduction in recurrence rate from 79% to 14%.[12]

As a palliative for symptoms, including relief of pain resulting from bone metastases and treatment of brain metastases, there is evidence in the literature that demonstrates significant benefit.

Other local treatments – interventional radiology

Given the relative lack of effectiveness in the treatment of adrenocortical carcinomas and their metastases, the use of interventional radiology techniques, with either percutaneous or intra-arterial approaches, is a resource that has been used in attempts to control the disease. However, once again, given the rarity of this pathology, the series described in the literature result from a small number of cases, a diluted sample created at the expense of other primary carcinomas, including hepatocellular carcinoma and metastatic colorectal neoplasms.

Radiofrequency ablation therapy may be an alternative for local recurrences and metastases, especially hepatic ones, provided they are smaller than 5 cm, in patients for whom surgery is not recommended. Its role as a palliative of pain, in the case of bone

metastases, has also been described.[10]

Chemoembolisation has also been used to treat liver metastasess.[9]

FOLLOW-UP

This should be conducted through clinical tests, analytical evaluation and imaging tests.

After initial surgery

It is necessary in the immediate postoperative period, especially in secreting tumors, particularly with the analytical evaluation of hypothalamic-pituitary-adrenal axis function. This evaluation not only enables the success of the surgery to be evaluated (complete or not) but also guides the hormone replacement therapy.

Long term

The determination of endocrine markers enables, in case of complete resections, the evaluation of recurrences and in the case of incomplete resections, to monitoring the profiles of hormone secretion, maintaining them at physiological levels.

Should be carried out at every 3 months and include cortisol (determination of urinary free cortisol and suppression tests with dexamethasone), androgens (dehydroepiandrosterone sulfate, androstenedione, testosterone) and 17-hydroxyprogesterone, based on the preoperative hormonal profile.[2]

The imaging tests should be carried out very carefully. For one year after surgery, a thoracic-abdominal CT scan is recommended every 3 months, and over the next 5 years, the test should be carried out every 3 to 6 months, and annually from then on.

In case of advanced disease, the determination of serum lactate dehydrogenase (LDH) may serve as a marker of disease progression.[23]

CLINICAL CASES

Clinical Case 1

Male patient, age 58, referred to our institution for bilateral adrenal nodules, associated with an elevation of serum estradiol levels, detected during the study of a bilateral gynaecomastia.

This is a patient with a history of type 2 diabetes mellitus, hypertension and multinodular goiter with lymphocytic thyroiditis, treated with metformin, gliburide, lisinopril, amlodipine and indapamide.

Subjectively, the patient had no significant complaints and, in addition to hypertension, only bilateral gynaecomastia was evident in the objective examination, with no other signs of feminization.

The hormone study carried out revealed that, in relation to the sex hormones, there was an increase in serum estradiol (220 pg / mL) and androstenedione (7.1 ng/mL) with a slight decrease in testosterone levels (total and free testosterone of 1.7 and 0.5 ng/mL, respectively), with progesterone and prolactin at normal levels. There were no visible changes in the other parameters, including serum glucose and mineralocorticoid, metanephrines and urinary vanillylmandelic acid levels.

Abdominal CAT scan revealed a nodular image in the left suprarenal gland, of 42 mm at the widest point, with fat density, and another on the right of about 15 mm, compatible with adenoma. The additional MRI confirmed only the left formation, with suspicious imaging features.

No other significant changes were apparent in either test, particularly adenopathies.

The patient was subjected to left adrenalectomy, and the pathological study confirmed the presence of a carcinoma of the suprarenal cortex, with subsequent normalization of hormone levels. The patient had no other adjuvant treatment.

Six months later, a new elevation of estradiol (61.5 pg/ml) was observed, but without evidence of recurrence in the CT imaging control.

The first imaging evidence for recurrence appeared in the second year after surgery, in the form of two nodules in the left suprarenal locus (each measuring 15 mm at the widest point). The patient was submitted to an exploratory laparotomy with multiple biopsies, with objectification of histological recurrence, and was kept under strict observation until a new intervention six months later, with microscopic total resection of the lesions.

The third evidence of recurrence appeared again six months later, in the form of multiple peritoneal nodules, one with pancreatic involvement, therefore complete surgery was not possible on this occasion. The patient was again submitted to surgery, but it was concluded that the lesions were unresectable.

Throughout this period, estradiol levels remained analytically high, without any other significant changes.

At this juncture, chemotherapy was proposed as a palliative treatment, starting with Berruti's cytostatic protocol (Etoposide/Doxorubicin/Cisplatin, in asso-

ciation with adrenolytic, mitotane).[19,20] A daily dose of 2g/day of mitotane was started.

Hormone supplement with hydrocortisone was begun in the fourth week after the start of treatment, although signs of adrenal insufficiency were not yet visible.

In the evaluation after the fourth cycle, the objective was to stabilize the disease, completing two more cycles, after which the patient was medicated only with mitotane.

The mitotanemia levels were monitored frequently, with a maximum value of 24mg/L. However, with serum levels of around 14mg/L (theoretically non-toxic levels), the patient developed progressive lethargy, confusion, ataxia and dysmetria, attributed to the Neurotoxicity of mitotane, after exclusion of acute neurological syndrome. The dosage was reduced. At lower levels, the patient reported only some gastrointestinal symptoms, such as nausea, sporadic vomiting, and diarrhea.

52 months after diagnosis, the disease was stabilized according to imaging tests, with fluctuations in sex steroid levels and lactate dehydrogenase (LDH).

Clinical Case 2

Female patient, aged 29 years, with no relevant history, with onset of abdominal bloating, postprandial fullness and progressive anorexia, accompanied by flushing episodes. At this point an upper gastrointestinal endoscopy was carried out, which showed changes consistent with chronic superficial gastritis, confirmed by biopsy.

Six months later, the patient developed episodes of epigastric pain with dorsal irradiation, which become increasingly frequent, prompting several trips to the emergency room. At this point, a palpable hard mass with regular contours was evident on objective examination, occupying the upper abdominal quadrants.

A thoraco-abdominal-pelvic CAT scan found a large ipsilateral mass between the liver and kidney measuring 25 cm at the widest point, and another in the left hypochondrial area with 10 cm at the widest point, both with heterogeneous uptake of contrast product and multiple foci of calcification in their interior. Two nodule images at the level of the hepatic parenchyma were also visible. It was concluded that there was a bulky tumor, with probable origin in the right adrenal gland, and liver metastasis.

Analysis revealed a thrombocytosis (Platelets: 444x10^3/µL), an elevation of LDH (1162 U/L) and of alkaline phosphatase (156 U/L), and from the in-depth hormone study, only slightly higher than normal urinary cortisol levels (287 µ g/24 h) and levels of delta - 4 - androstenedione and dehydroepiandrosterone sulfate (DHEA-S) also higher than normal (31.7 ng/ml and 817 µ g/dL) were observed.

To clarify the etiology of this formation, it was submitted to aspiration biopsy of the mass, which was consistent with carcinoma of the adrenal cortex.

On evaluation of the surgical conditions, we concluded that the lesion was non-resectable due to the absence of cleavage planes with the liver.

The patient started palliative chemotherapy with a combination of Doxorubicin/Cisplatin and Etoposide, associated with mitotane, at an initial dose of 1.5 g/day. Support treatment with hydrocortisone and fludocortisone was begun immediately, with the first cycle, and adjusted over the treatments based on the clinical practice, ionogram and hormone levels.

The main toxicities were essentially anorexia, nausea and vomiting grade II/III (WHO scale), mixed dyslipidaemia and anemia grade II/III requiring transfusion. A progressive weight loss was also observed (about 7%).

On evaluation at the end of the third cycle, imaging showed stabilization of the disease, therefore the chemotherapy was continued, this time without doxorubicin, but with increasing levels of cisplatin (100mg/m2 day 1 of the cycle) and etoposide (100 mg/m^2 days 1 to 3 of the cycle) due to the toxicity presented. Two more cycles of these combinations were completed.

Mitotane doses were increased gradually, under monitoring of serum determinations, with the patient showing toxic levels (maximum of 31 mg/L) at a dose of 8 g/day. With these levels the patient developed neurological symptoms, with lethargy, psychomotor slowness, and speech difficulties.

The patient later joined an American Research Center, and a protocol for clinical trial of an antiangiogenic. She died approximately 4 months later. Her survival was approximately 23 months.

FINAL CONSIDERATIONS

Due to their rarity, carcinomas of the suprarenal cortex remain a neoplasm that is difficult to treat.

Despite the poor prognosis, more recent series report more and more cases diagnosed in the earlier

stages, partly due to the improved accuracy and accessibility of diagnostic tests.

Referral to centers with expertise in this pathology is essential to maximize the success of the available therapies.

The results of the large, randomized FIRM-ACT trial, which is expected to last seven years, could bring news in terms of future guidelines for the treatment of advanced disease, but the great hope lies in the deepening knowledge of the molecular mechanisms of its tumorigenesis and the development of targeted therapies. ■

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