

Sindrome di Cushing e carcinoma surrenalico.

Caso clinico



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Cushing syndrome and adrenal carcinoma: clinic case

A 21 year-old girl arrived at our hospital with a short history of hirsutism, facial plethora, amenorrhea, progressive weight gain and hypertension..

The clinically suspected Cushing syndrome was then confirmed through chemical pathology.

In fact, the results from haemato-chemical exams were: 45.5 μ g/dl cortisol, a DHEA sulphate > 8000 ng/ml, 7.2 pg/ml ACTH, 17OH-Progesterone 10.66 ng/ml, Delta-4 Androstenedione 5.2 ng/ml, UFC (Urine Free Cortisol) > 1000mg/24h, FSH 0.8 mUI/ml, LH <0.1 mUI/ml, Prolactin 13, 17,estradiol 96 pg/ml, and a bonded hypokalaemia, K⁺ 2,4 mEq/L. The echogram of the complete abdomen reveals, near the superior pole of the left kidney, the presence of a solid mass, not independent from the pole itself, about 9.5 centimetres long, diagnosis confirmed to the TC abdomen and pelvis too, with or without mdc.

This removed mass resulted, from the histological exam, in an adrenal carcinoma with a general and trabecular structure.

Primal adrenal tumours are responsible for about 10% of Cushing syndrome cases. They present an annual incidence of 0.5 - 2.0 cases per million of inhabitants.

The prognosis of adrenal ca remains low, with 5 year survival rate for 38% of diagnosed patients.

KEY WORDS: Adrenal carcinoma, Adrenal gland, Cushing syndrome.

Introduction

The Cushing syndrome is an hormonal disorder provoked by cortisol hypersecretion on the part of the adrenal glands.

The production of cortisol is produced by hypersecretion of ACTH on the part of the hypophysis or a non-endocrine tumour. The primal defect is probably represented by the development of an hypophysial adenoma, usually a benign tumour. Some tumours, both benign and malignant, arising out of the hypophysis cerebri, can produce ACTH. This condition, known as ACTH ectopic syndrome, can be unleashed, i.e. from the small cell pulmonary carcinoma.

10-20% of patients affected by Cushing syndrome pre-

sent, instead, a tumour at the adrenal glands, benign in most cases, while it is rare to notice an adrenal carcinoma.

Cortex of suprarenal carcinoma is a rare malignant tumour, with a valued annual incidence of 0.5 - 2.0 cases per million of inhabitants yearly ¹.

The prognosis of adrenal ca remains low, with a 5 year survival rate of 38%.

Anyway, this rate has strongly improved after 1988 ².

This condition is due to a lack of data on its natural history and response to therapy, despite the improvements in clinical detection and molecular understanding. The most common syndrome related to adrenal tumours is Cushing Syndrome, reported in 30-40% of patients affected by adrenal tumour ³.

The adrenal-cortical carcinoma can develop at any age in both males and females ⁴.

According to known data, it occurs more frequently among women (62.5% - 72.1%).

The patient's age seems to be very important in adrenal carcinoma, as it probably influences the prognosis.

Many studies have underlined that children with prog-

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nosis of not-metastasizing adrenal carcinoma have better prognosis after complete tumour resection than adults with same pathology and same treatment ⁵⁻⁶. Adults show a tendency towards a more aggressive tumour with a shorter prognosis ⁷⁻⁸⁻⁹⁻¹⁰. These two issues suggest that young adults have a better prognosis than patients who are over 40 ¹¹.

Adrenal tumours can be classified according to the following:

- functional (FT) when hormonal secretions cause clinical consequences: Cushing Syndrome (CS), Virilization Syndrome (VS), Feminization Syndrome (FS), or a mixed-syndrome, Cushing-Virilization (CVS);

- non functional (NF) if there is no secretion of excessive hormones or if insufficient hormonal precursors and/or active hormones are produced. Such tumors can still secrete excessive imports of the steroids noticed during laboratory assessments ¹². It should be noted that androgen-secreting tumors in men and estrogen-secreting tumors in women may not result in clinically significant syndromes, and both could be considered as NF.

Due to low incidence of adrenal tumours in specialized medical centres, it has been hard to gain experience with their diagnostics and treatment. Adrenal carcinoma is a rare tumor that becomes apparent in advanced stages.

Stage at diagnosis is a relevant prognostic factor, while age, sex and tumour functions are not.

Complete resection is the only effective treatment with the value of mitotane and other medical therapy yet to be determined.

Case report

A 24 year old woman, with a past story of primal hypothyroidism treated with Eutirox 50Å, then augmented to 75Å and finally suspended, after about 2 years. In January 2006 the patient, due to polyphagic nutrition troubles with consequent body weight increment, is referred to a specialist; he suggests her a low-calorie diet with occasional som-

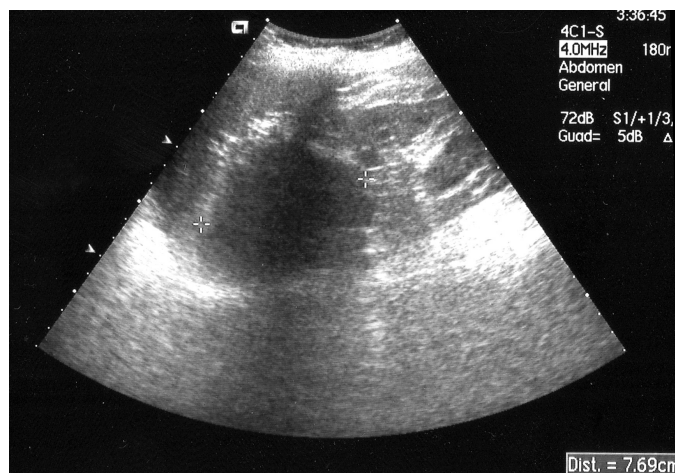


Fig. 1: Abdomen and pelvis ultrasonography.



Fig. 2: TC abdomen and pelvis with mdc lateral projection.



Fig. 3: TC abdomen and pelvis with mdc.

ministration of homeopathic and/or adjuvant in slimming-regime diets. In subsequent months, an evident swelling of the face, increasing thinning of body members and of hairs.

In April a bad deterioration of the these symptoms occurs; it clearly reflects hypercortisonism with amenorrhea, venous reticulum on the back of lower limbs, petechias and strong astenia. The patient is then admitted in September at another centre, where she receives haematochemical and instrumental exams.

The ultrasonography of entire abdomen shows, the presence of a solid mass near the left kidney superior pole not independent from the pole itself, about 9.5 centimeters long (Fig.1).

Subsequently performed TC with and without contrast medium describes, in the left kidney pole, an isothick oval gross formation, with bossed borders and a maximum dimension of about 10 cm. The lesion marks the spleen postero-inferior profile and it acquires a good and homogenous contrasto-graph impregnation after injection of mdc ev (Fig. 2 and 3).

She is then discharged with the following diagnosis: left adrenal neoplasia and primary amenorrhea with related Cushing Syndrome.

In October the patient arrives at our centre, in good clinical conditions, with high pressure values almost pointing to commencement of hypertension (150/100 mmHg) and increasing asthenia.

After the objective exam she exhibits "facies lunaris" skin thinning, hypertrichosis, edemas, alopecia, "gibbus" on the neck, obesity to the trunk.

The patient is referred to cardiological consulting; after ECG and Echocardiogram, we notice labile hypertension, sinus rhythm with low R progression from V1 to V3.

We proceed with another echogram of entire abdomen that confirms the presence of the above mentioned formation on the back of the left adrenal gland, about 10 cm. long, without evidence of repetitive lesions to the liver.

The patient undergoes hormone determination: plasmatic cortisol 45.5 μ g/dl (range am 6.8-26.3 – pm 3.8-14.4); DHEA Sulphate > 8000 ng/ ml (range 0.07-3.48); ACTH 7.2 pg/mL (up to 60); 17OH-Progesterone 10.66 ng/ml; Delta-4 Androstenedione 5.2 ng/ml; Urine Free Cortisol (UFC) > 1000mg/24h (range 30-100), FSH 0.8 mUI/ml; LH <0.1 mUI/ml; Prolactin 13; 17,estradiol 96 pg/ml.

Tumor markers were also measured, particularly CEA and α -fetoprotein, which resulted as standard (2.8ng/ml and 4.6 ng/ml respectively).

Haematochemical exams indicate hypokalaemia, K⁺ 2,4 mEq/L (range 3.50-5.30), while other parameters are standard.

After evident asthenia, disinhibition and difficult concentration the patient underwent neurological and psychiatric counselling which, respectively, revealed an hypasthenia to the lower limbs with positive Lasegue mainly on the left and a "reactive" depressive condition. The patient was then balanced with aspartate potassium, 10mEq/h and Aldactone 200mg.

After a painstaking study, it is time for a surgical operation.

A central venous catheter, a nasogastric intubation and a bladder catheter are placed. The patient is dorsally positioned bedsores on a table broken under the costal border; we then proceeded to make an infracostal incision on the left, then enlarged on the right; peritoneum and parieto-colic douche was opened, to overturn colon and spleen and to expose the 15-cm-diameter formation on the back of the adrenal gland that apparently does

not infiltrate kidney and other contiguous structures.

We proceed with ligature and section of adrenal venous and arterial vessels, and with removal of the left adrenal gland, following the usual technique. After an accurate haemostasis, a tubular counterpuncture drainage is performed. A muscular plan reconstruction with multiple layers is then carried out. Subcutis and cutis in monofilament 4/0.(Fig. 3 and 4)

Patient's postoperative course has been completely regular.

Nasogastric intubation and vesicular catheter were removed on the same oppure the next day; Bowel canalization was obtained on the 3rd postoperative day and the patient was able to eat regularly.

Soon after postoperative course, the patient begun infusion therapy of hydrocortisone ev (100mg/6ore) until the third day, when she started oral therapy with acetate Cortisone, 25 mg 1 cp every 6 hours.

The Kaliemia value was checked daily for any further therapy.

The plasmatic cortisol gradually decreased: first day, 28.9 μ g/dl; second day, 22,7 μ g/dl; third day, 13,3 μ g/dl; until discharge when the value was about 11.1 μ g/dl.

The microscopic histological test showed a global multinodular structure with different sizes, strong plesiomorphism with large areas occupied by little ovoid cells, with low grade of cytoplasm and strange core, a number of micro and macronecrosis groups and embolisation of some vessel cells. In conclusion, it is a trabecular and general adrenal carcinoma. Neoplastic embola, capsule and peri-capsular fatty tissue infiltration.

The patient was discharged after 9 days, and transferred to the endocrinology section of our Faculty. She undergoes daily check lettings, and CLU is monitored. She has had a PET-TC and her daily 4cp doses of acetate Cortisone were gradually reduced to 2 cp daily.

Discussion

The age incidence of adrenocortical carcinoma appears to be bimodal, with a peak occurring in the first decade and a second peak occurring in the fourth decade. In the current series, adrenocortical carcinoma was far more prevalent in women than in men (4:1) ¹³.

Adrenal carcinoma is rare, it has an incidence value between 0.5 and 2/ 1 per 10⁶ in habitants.

The most common manifestations in patients with adrenal ca are: weight augmentation/ centripetal obesity, muscular hypotrophy, hypertension and acne. Hirsutism and oligomenorrhoea are often present in patients with an element of virilization.

Cushing syndrome (30.4%) is the most common clinical manifestation ¹⁴.

The grouping of Cushing syndrome and virilization is about 24% of the population affected by adrenal carcinoma.

Bertagna and Orth reported that virilization is a characteristic differentiating Cushing's syndrome due to adrenal carcinoma from Cushing's syndrome due to adenoma¹⁴.

The theory is that androgenic steroid excess develops in patients with adrenal carcinoma because androgenic steroid precursors are not converted to glucocorticoids as efficiently as in those with adenoma. However, Daitch et al observed that, while most patients with adrenocortical tumors presented with mixed endocrine abnormalities (including virilization), most patients with adenoma also presented with mixed endocrine syndromes¹⁵. Virilization alone has been reported in 20% to 30% of patients with functional adrenocortical carcinoma¹⁶.

But there is a difference between adults and children, with 3-5%¹⁷ in adults and 72% in children¹⁸. In women, virilization shows itself with oligomenorrhoea, hirsutism, cystic acne, muscular mass augmentation, libido reduction and clitoromegaly. Feminization and hyperaldosteronism are much less common (65 and 2.5% respectively)¹⁹.

Hormonal evaluation can also be useful to monitor patients with adrenal carcinoma.

Hypercortisonism is better valued thanks to Urine Free Cortisol (UFC/24h).

Orth recommends 2, 3 consecutive measurements for urine cortisol in the 24h urine sample²⁰. More than 90% of patients with Cushing's syndrome, have CLU > 200lg/24h, considering that 97% of healthy patients have values < 100lg/24h.

Ideally the way to determine whether a patient has adrenocorticotrophic hormone (ACTH) dependent or independent hypercortisolism is the concurrent measurement of plasma ACTH and cortisol by 2-site immunoradiometric tests. If plasma cortisol is greater than 50 µg/dl. and ACTH is less than 5 pg/ml., cortisol secretion is ACTH independent and the patient has a primary adrenal problem. In contrast, if plasma ACTH is greater than 50 pg/ml., cortisol secretion is ACTH dependent and the patient has Cushing's disease, ectopic ACTH or the corticotropin releasing hormone

syndrome. If the 2-site immunoradiometric assay is not available, the classic high dose dexamethasone suppression test (2 mg. every 6 hours for 2 days) can be done to differentiate pituitary from adrenal Cushing's syndrome. In patients with adrenal adenoma carcinoma plasma and urinary free cortisol fail to be suppressed. Several plasma and urinary steroids are elevated in Cushing's syndrome as a result of functioning adrenocortical tumors. Another consideration in the natural history of adrenal cortical carcinoma is the association with other tumors or pathologies.

Venkatesh et al.²¹ published a series of 100 patients with adrenal carcinoma and showed that 13 patients had a second primary tumor and one patient had a third tumor. The most frequent secondary tumors appeared to

be breast carcinoma, thyroid carcinoma, and melanoma. Adrenal cortical carcinoma also has been described in families with histories of other types of tumors²².

The relationship between adrenal cortical carcinoma and congenital malformation, like hypertrophia and visceromegaly, has also been described²³⁻²⁴.

Staging system for patients with cortex of suprarenal carcinoma, originally proposed by MacFarlane²⁵ and then modified by Sullivan²⁶ and others, is frequently used. First and second stage patients have a tumor limited to the adrenal gland without local invasion or distant metastasis, and a tumour size under 5 cm (stage I) or 5 cm (stage II), respectively.

Patients with Stage I and II disease presented with tumor confined to the adrenal gland without local invasion or distant metastases and with a greatest tumor dimension of .5 cm (Stage I) or .5 cm (stage II), respectively. Patients with these tumors have the best chance of cure with surgical excision. When there is local tumor invasion that does not involve adjacent organs or regional lymph nodes, the tumor is considered to be Stage III. In Stage IV disease, there is distant metastases or invasion into adjacent organs plus regional lymph nodes. In the majority of reports of adrenal carcinoma, the tumors generally are in an advanced stage (Stage IV) of disease. In the review of Wooten and King²⁷ studies, 3% of patients is classified with phase I, 19% with phase II, 29% is classified with phase III and 49% with phase IV of the disease.

Richie and Gittes²⁸ have noticed that, mainly in male patients, diagnosis is made in the most advanced phases, while in women it is made in the early ones.

Younger patients tend to have the disease in the first tumour phases. In children very few cases of phase IV-adrenal carcinoma have been detected, and this probably explains the much better prognosis in comparison with adults. The relationship between the phase of disease and the survival after diagnosis doesn't seem to have an impact on the difference for phase I and II, but a great reduction of survival rate with the phase IV and an intermediate survival rate with phase III has been observed. The overall 5-year survival rate after diagnosis was 15% to 47%²⁹⁻³⁰. Most series showed no statistically significant differences in survival based on patient age, gender or tumor functional status. However, stage was a significant prognostic factor. For stages I to IV tumors approximate 5-year survival was 30% to 45%, 12.5% to 57%, 5% to 18% and 0%, respectively. Highly aggressive and unresectable tumors progressed rapidly within a few months. Surgical resection was the only therapy for adrenocortical carcinoma that significantly prolonged survival, particularly when disease was detected at stages I and II. Median survival in patients with unresectable tumors was 3 to 9 months, whereas after complete resection median survival was 13 to 28 months.

Imaging is the key to diagnosing adrenal carcinoma. Ultrasonography of the adrenal gland has proved to be

effective for identifying adrenal masses but it is limited by dependence on operator skills and patient body habitus. Xiao et al reported an 87% detection rate with a false-negative rate of 12%³¹. Most adrenal tumors appear as smoothly rounded, solid masses replacing the usual triangular or crescent configurations of the adrenal gland. Moreover, ultrasound can identify the displacement of adjacent structures

caused by the tumor. Several groups have imaged adrenal masses 1.3–3.0 cm using conventional scanning techniques. Most adrenal neoplasms appear as smoothly rounded, solid masses replacing the usual triangular or crescent configuration of the normal adrenal gland. Furthermore, US can identify displacement of adjacent structures caused by the tumor. The use of decubitus positions and oblique scanning planes for aligning the adrenal gland between kidney and aorta or inferior vena cava has resulted in remarkable image improvement. In some cases, US imaging has proven helpful in visualizing inferior vena caval (IVC) displacement and/or invasion.

Computerized tomography (CT) is considered the diagnostic study of choice for evaluating adrenal masses. Because of surrounding adipose tissue in the retroperitoneum, adrenal glands are easily visible on CT. On thin section CT nodules as small as 3 to 5 mm. can be identified.

Xiao et al³¹ reported a 98% detection rate with less than a 10% false-positive and negative rate. CT provides information on size, homogeneity, calcification, the area of necrosis and the extent of local invasion. Many groups have attempted to differentiate benign versus malignant adrenal masses based on size.

Almost every author has tried to differentiate benign and malignant adrenal masses according to dimensions.

Beldegrum and coll³² observe that 92% of adrenal carcinoma are bigger than 6 cm; the most authors agree in considering malignant those lesions that are 5cm-or-more in size, with bossed borders, irregular outline and an heterogeneous contrast augment.

Many authors have attempted to differentiate benign versus malignant adrenal masses on the basis of size, indicating that lesions ≤ 3 cm probably are benign, whereas lesions > 5 cm probably are malignant.

However, there is much overlap, and masses between 3 cm and 5 cm fall into a "gray" area of clinical decision making³³⁻³⁴. Because tumor size is a function of duration, it is clear that the malignant nature of an adrenal mass cannot be predicted on the basis of size alone. Thus, attenuation, consistency, and contrast enhancement have been considered as more reliable discriminators between malignant and benign adrenal tumors. Malignant adrenal lesions tend to be larger in diameter (3 cm), present with blurred margins and irregular shape, and more often demonstrate inhomogeneous contrast enhancement, whereas benign masses are smaller (3 cm), have sharp borders, and exhibit homogeneous enhancement³⁵.

Recently, some authors have advocated that the attenuation value of an adrenal mass on unenhanced CT scans

can distinguish between an adenoma and a nonadenoma.

In the series by Korobkin et al.³⁶, all adrenal masses with an attenuation value ≤ 18 HU were adenomas. According to Lee et al.³⁷, adrenal lesions with attenuation values ≤ 0 HU need no further work-up, because these lesions have been shown to be adrenal adenomas.

In regards to treatment of patients with cortex of suprarenal carcinoma, little has changed. It is still a difficult issue.

The surgical treatment of patients with adrenocortical carcinoma is still a subject of some controversy³⁸⁻³⁹.

Complete surgical excision is the best chance of cure for patients with Stage I and II tumors and in children. The presence of IVC invasion should not be considered as metastatic disease but, rather, as tumor extension. In such cases, surgical procedure should be more aggressive, attempting to remove completely the intravascular extension⁴⁰⁻⁴¹. The indication for total (or near-total) tumor excision in patients with Stage III and IV disease remains controversial. Some studies suggest a benefit from maximal debulking of the tumor mass when complete surgical excision of the tumor is not possible⁴². Conversely, there some series clearly indicate that surgical palliation does not influence the survival of the patients

The Mitotane, DDT isomer, remains a therapy support, but this drug's usefulness is limited by relative severe toxicity and by the lack of definite proof of life extension. Multicentric studies have been made to evaluate the main prognostic factors of mortality, in the hope to confirm the positive role of surgery and mitotane therapy.

Riassunto

Una giovane donna di 21 anni si è presentata presso la nostra struttura con una storia breve di irsutismo, plethora facciale, amenorrea, guadagno progressivo del peso ed ipertensione..

La sindrome di Cushing ritenuta sospetta clinicamente è stata confermata poi biochimicamente.

Dagli esami ematochimici eseguiti di è riscontrato infatti: un Cortisolo plasmatico di 45.5 Ig/dl, un DHEA Solfato > 8000 ng/ ml, l'ACTH di 7.2 pg/ml, 17OH-Progesterone 10.66 ng/ml, Delta-4 Androstenedione 5.2 ng/ml, Cortisolo libero urinario (CLU) > 1000 mg/24h, FSH 0.8 mUI/ml, LH < 0.1 mUI/ml, Prolattina 13, 17,estradiolo 96 pg/ml, ed inoltre un ipopotassiemia franca, K⁺ 2,4 mEq/L.

L'ecografia dell'addome completo evidenzia in prossimità del polo superiore del rene di sinistra la presenza di una massa solida mal dissociabile dal polo stesso delle dimensioni di circa 9.5 cm., diagnosi confermata anche alla TC addome e pelvi con e senza mdc.

Questa massa asportata si è dimostrata essere all'esame istologico un carcinoma del surrene a struttura trabecolare e diffusa.

I tumori surrenalici primari sono responsabili del 10% circa dei casi della sindrome di Cushing. Presentano un incidenza annuale valutata a 0.5 - 2.0 casi per milione d'abitanti all'anno.

La prognosi del ca surrenali rimane bassa, con una sopravvivenza a 5 anni del 38%.

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