

Feminizing adrenal tumors: Our experience about three cases

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ABSTRACT

Feminizing adrenal tumors (FATs) are very rare as they account for less than 2% of all the adrenal neoplasms. Their prognosis is deemed to be very poor. We aimed to present a mono centre (adult and pediatric) experience over a long period of time (January 1980 to Jun 2012). During the study period, we observed only three cases in men aged 22 (2 cases) and 45 (1 case). They all consulted for a painful gynecomastia, decreased libido and impotency. Estradiol was high in two cases at presentation, and after a relapsing tumor in the third one. All had big adrenal tumors (5.9, 6, and 17 cm), and a mixed secretion composed by high estradiol and cortisol. The pathological study argued for malignancy in two cases. But, only one had diffuse metastasis and died 4 years after diagnosis; the others diagnosed one and three years ago are still alive without any metastasis or relapsing.

Key words: Adrenal, feminizing tumors, gynecomastia, hypogonadism

INTRODUCTION

The term of feminising adrenal tumors (FATs) is used to describe tumors secreting estrogens especially in men. These tumors are uncommon as they account for only 0.37-2% of all adrenal tumors.^[1]

Clinical manifestations are breast problems such as gynecomastia or breast tenderness with or without other manifestations of gonadal deficiency. Sometimes a huge abdomen tumor is observed. When they occur in children, they induce pseudo puberty (isosexual in girls and heterosexual in boys). They are exceptional in pre-menopausal women. In the post-menopausal period, their main manifestation is genital bleeding.

In these tumors, the difference between adenoma and

carcinoma is uneasy, except if metastases are already present. Malignant tumors are supposed to have a dire prognosis.^[2] Our aim was to report our experience about three cases observed over a long period of time (January 1980 to June 2012) in a department dealing with pediatric and adult endocrinology.

CASE REPORTS

Case 1

A male patient aged 22 consulted for the first time on February 1983 for recent breast enlargement with back pain, decreased libido, and erectile troubles. Clinical examination was normal except for mild gynecomastia. Hormonal exploration done by his family physician showed normal prolactin (PRL)=5.9ng/ml (n=5-10), low testosterone (T)=2ng/ml (n=2-9), normal folliculostimulating hormone (FSH)=4.3mu/ml (n=2-9), normal luteostimulating hormone (LH)=9.2mu/ml (n=2-11) and normal estradiol (E2)=30pg/ml (n=10-40). Radiological exams argued for a left adrenal tumor measuring 6 cm in height. Unfortunately, cortisol assessment was not done. After surgery, histological examination confirmed the adrenal origin and argued for a malignant one with a small metastasis in the homolateral kidney. Two months later, cortisol assessment was normal (70ng/ml, n = 50-250), but E2 and dehydroepiandrosterone sulphate (DHEA S) were in the

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pathological ranges [respectively, 66.9 pg/ml ($n < 40$) and 3.2 ng/ml ($n = 0.5-2.5$)], then a small polylobulated tumor appeared in the liver. Eighteen months later, mean cortisol was slightly elevated (279 ng/ml), but was suppressed by 2 mg dexamethazone (18 ng/ml), the corticotrophin hormone (ACTH) was undetectable, E2 was high (346 pg/ml), so were plasma 17-hydroxy progesterone (17OHP): 11.46 ng/ml ($n = 0.5-2.5$), and DHEA S (6.34). Numerous metastases were present in the liver, chest, right adrenal, and bones [Figure 1]. Abdomen lymph nodes were involved too. He died 4 years after the first symptoms, as OP'DDD was not available and classical chemotherapy was inoperative.

Case 2

A male patient aged 45 complaining of fatigue, anorexia, decreased libido, and ejaculations consulted in 2009 for an aching gynecomastia. On clinical examination, there was a moderate bilateral gynecomastia [Figure 2] without galactorrhea.

He did not have any sign of cortisol excess. His BMI was equal to 21 kg/m². Systemic blood pressure was normal. Body hair repartition and testis volume were slightly decreased.

Abdominal ultrasound showed a huge tumor measuring more than 17 cm above the left kidney that was compressed. Computed tomography (CTscan) confirmed the diagnosis of the left adrenal tumor reaching the parietal area, without invasion of adjacent organs [Figure 3].

Biological exams showed a sub clinical hypercortisolism [220 ng/ml (50-250)], that failed to be decreased after 2 mg dexamethasone (40 ng/ml), hypogonadism with normal FSH and low LH [$T = 5.66$ nmol/l ($n = 8-34$), FSH = 1.19 mu/ml (1-10), LH = 0.03 mu/ml (1-9)], and normal prolactin = 225 μ UI/ml ($n < 454$). E2 was very high varying between 304 and 451 pmol/ml ($n < 50$). DHEA S, 17OHP, and D4Androstenedione (D4A) were high too [respectively, superior to 10.000 ng/ml ($n: 1450-3670$), 7.79 ng/ml (0.3-3 ng/ml), and 10.3 nmol/l (0.9-6.5)]. He was operated on, and the huge tumor was totally removed [Figure 3b].

Histological examination described an endocrine tumor with a thick capsule which was infiltrated in some areas. The architecture was trabecular, and alveolar or organized in nests. Tumoral cells were polymorphous with

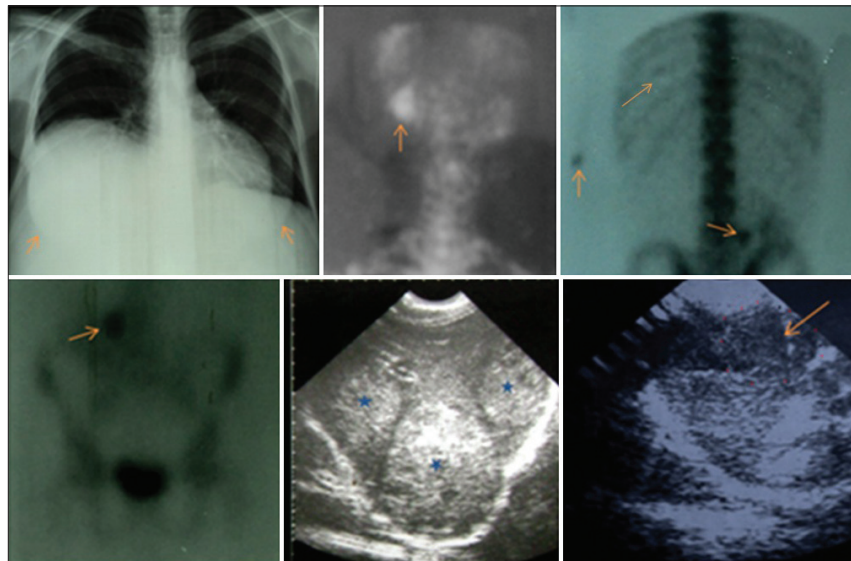


Figure 1: Bilateral gynecomastia, and diffuse metastases (bones, right adrenal, and liver)



Figure 2: Bilateral gynecomastia confirmed by mammography

granulated cytoplasm and polymorphous nuclei (round, egg shaped and sometimes huge). Vascular embolisms were present.

One month after surgery there were a weight gain, normalization of E2 (12pmol/l) and other parameters such as T (11.4 nmol/ml), D4A (1.64 ng/ml, $n = 0.8-3.1$), DHEA S [249 ng/ml ($n = 133-441$)], and 17OHP [2.8 ng/ml (1.5-7.2)]. Cortisol was suppressed by dexamethazone test. Radiological explorations were normal too. Three years later, there is not any relapsing.

Case 3

A man, aged 22, consulted in 2011 for bilateral gynecomastia that began 3 years before, with recent fatigue, decreased libido and erections, and reduction in shaving frequency. Clinical examination showed bilateral gynecomastia [stage 2: Figure 4] without galactorrhea.

He was weighing 68 kg for 1.74 m (BMI = 22.66 kg/m²), blood pressure = 120/80 mm Hg, heart frequency = 74 bt/min and body hair repartition was normal; his penis was pale and measured 5 cm in length. Testes diameters were normal. Abdomen palpation did not find any mass. The rest of physical examination was normal.

Routine analyzes were unremarkable. Hormonal assessment showed very high estradiol (1722 pg/ml)

with low testosterone (0.47 ng/ml: $n = 2.4-8.3$), low FSH (<0.1), low LH (0.6) and high 17OHP (26.9 nmol/l; $n = 0.9-6.7$). Prolactin rate was slightly elevated: 26 ng/ml (normal ranges: $n = 4-15$). Cortisol was normal, but failed to be suppressed by 2 mg dexamethazone (193 µg/l → 194). DHEA S and androstenedione were not increased (respective values: 361 µg/dl, $n = 133-441$ and 2.44 ng/ml, $n = 0.3-3.1$).

Abdomen and pelvis ultrasounds showed a hypochoic right adrenal with small calcifications and normal testes measuring 38 × 13.5 mm.

CT scan confirmed a well-vascularized tumor measuring 59 × 43 × 56 mm situated above the right kidney [Figure 5]. Its spontaneous density was superior to 10 HU with an absolute «Wash out» equal to 60%. Many abdominal lymph nodes were present, but the liver was normal. The left adrenal was normal too.

Chest X-rays, chest CT scan, and body scintigraphy were normal. When he was operated on, the surgeon observed a well-limited, much vascularized mass. The kidney was slightly compressed, but not involved.

Histological study argued for a benign tumor with a Weiss score equal to 2 and a Ki67 <1%.

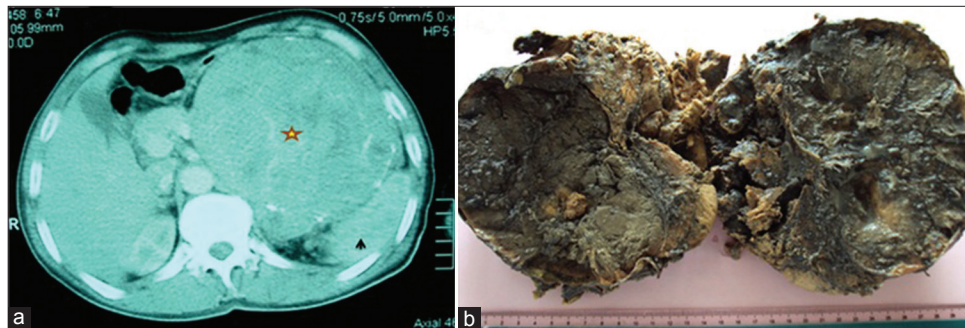


Figure 3: (a) CT scan showing a huge heterogenous tumor (star), above the left kidney (black arrow), reaching the parietal area. (b) macroscopic aspect

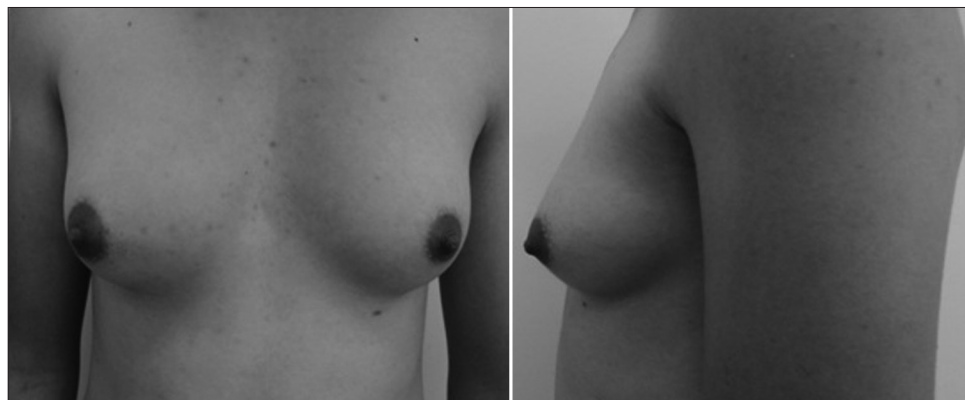


Figure 4: Bilateral and symmetrical gynecomastia (stage 2)

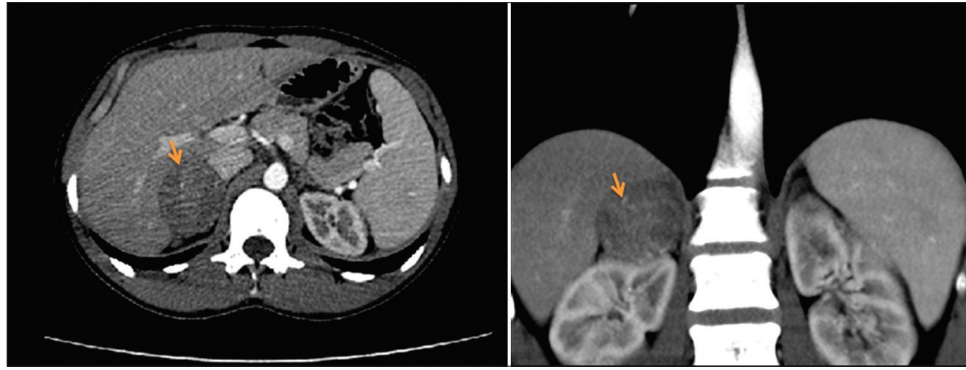


Figure 5: Right heterogenous and well-vascularized adrenal mass measuring 59 × 43 × 56 mm

Some months after surgery, the gynecomastia decreased in size and sexual behavior increased, radiological and hormonal exams were normalized, but a moderate systemic high blood pressure appeared. Successive explorations are still normal, but the time is not sufficient to exclude the malignancy.

DISCUSSION

Feminizing adrenal cortical tumors are extremely rare,^[1,3,4] as only a few cases have been reported so far. According to surgical large series, they account for less than 2% of all adrenal tumors.^[1] They are almost always malignant even if they seem benign at presentation. But, except relapsing and metastases, there are not any clinical, radiological and even histological criteria that distinguish benign from malignant tumors.

On the hormonal aspect, FATs are characterized by secretion of estrogens^[5] or by a mixed secretion.^[4] Their association to overt or sub clinical hypercortisolism is more common than androgens,^[4] aldosterone, or inhibin cosecretion in both males and females.^[6,7] The hormonal secretion is generally autonomous as in other adrenal tumors, but in some cases, it is stimulated by ACTH^[8] and suppressed by dexamethasone.^[9]

Feminizing adrenal neoplasms are usually seen in adult men. Their frequency seems more important in men over 70 (7%) than in those under 30 years old (1%). They are very rare in women^[10] and children,^[5,11,12] and exceptional in newborns.^[13]

Although, the mechanism of FAT is still unknown, some authors discuss a mutation in suppressive gene tumor located in 17p13 chromosome^[14] as in other adrenal tumors.

The main clinical signs in men are gynecomastia, decreased libido and erections, or ejaculation problems.

Gynecomastia without galactorrhea is generally the first symptom. It is usually bilateral and painful especially at the beginning. Breast development is rarely unilateral, but can precede an absolute increase of plasma estrogens as in our first observation. Its association with erectile troubles is classical, even in subjects with normal testosterone rates. Hair body repartition and testes may remain normal, but shaving frequency might be decreased.

Sometime other signs may be present such as fatigue, cachexy, fever, anemia, jaundice, and hematuria when the liver and kidneys are involved. Abdominal tumor may be huge as in one of our observations. But, as the tumor is profound and retroperitoneal, it is rarely found by palpation, especially in obese patients. But, in advanced stages, abdomen mass or its metastases may be easily discovered by clinical examination. Sometimes high blood pressure maybe present even in young people.

Feminization results from the imbalance between high estrogen and low free androgens. Hyperestrogenism results from both peripheral androgens conversion and direct estrogen production from an adrenocortical tumor.^[15] 21 OHase, 3 beta- ol-deshydrogenase, and 11beta OHase-acquired deficits are responsible of an increase in some precursors such as androstenedione, 17OHP, and DHEA S that are converted to estrogens via an increase in aromatase activity.^[16] As a consequence of estradiol excess, there is also an inhibition of pituitary function^[17] especially for FSH.^[6,7,16] Gonadotropins inhibition may also be increased by inhibin production by the tumor.^[6,7] Low free testosterone may be a consequence of an increase in sex hormone binding globulin (SHBG) too. The resulting hypogonadism is responsible for fatigue and reduced sexual behavior. A direct action of estradiol on the testis is another theory explaining a decrease in testes volume as observed in some cases. Another consequence of high estrogens is represented by a moderate increase in rate of prolactin secretion as in our third observation. Osteoporosis does not seem to be very important in subject with FATs probably

because of the increase in estrogens that protects bones from demineralization. High blood pressure observed in some young people seems to be related to an increase in aldosterone secretion by the tumor or to an increase in Renin precursors' synthesis by the liver.^[9]

For the outcome, FATs, treated or not, are supposed to have a dire prognosis as only two reported cases survived 10 years after the feminizing tumor was diagnosed.^[1] Some authors tried to define clinical, hormonal and radiological predictive factors for malignancy that are the same for all adrenal cortical tumors. These factors are: Tumor size superior or equal to 6 cm, CT scan positive contrast and wash out, necrosis lesions and calcifications, and organ compression. For feminizing tumors, very high estradiol and estrone, androgen precursors, and mixed secretion argue for the worst prognosis.

Histological predictive factors for malignancy are classified by Weiss^[18] on three stages. The tumor is considered as malignant if there are more than four suspect signs which are: Large nuclei, mitotic index superior to 5/50, atypical mitosis, light cells less than 25%, capsular invasion, necrosis, diffuse architecture (superior to 33%), sinusoidal invasion, and vascular embolism. But, some authors think high mitotic index and reduction in light cells are the most predictive factors. But there is no certainty.

For treatment, the gold standard is surgery as in other adrenal tumors. The tumor should be removed in one bloc by an open laparotomy to avoid partial surgery and metastatic diffusion when its size is greater than or equal to 6 cm. For medication, there is no specific treatment for FATs. Some physicians continue to use anti cortisol products such as OP'DDD (dichloro diphenyl dichloroethane) or mitotane and aminoglutetimide, in the post-operative period, as in other adrenal tumors. But it seems that the results are not very good. Ketoconazole has also been used.^[19] Chemotherapy with some new products does not seem to be better than the old scheme.

Some authors suggest use of new aromatase inhibitors^[3] to reduce aromatase activity and estradiol production, but this new therapy needs time to be evaluated, especially for the tumoricide action.

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