Review Article

# Feminizing adrenocortical tumors: Literature review

**Farida Chentli, Ilyes Bekkaye, Said Azzoug**

*Department of Endocrine and Metabolic Diseases, Bab El Oued Teaching Hospital, University of Medicine, Algiers, Algeria*

## ABSTRACT

Feminizing adrenal tumors (FAT) are extremely rare tumors prevailing in males. Clinical manifestations are gynecomastia and/or other hypogonadism features in adults. They are rarer in pediatric population and their main manifestation is peripheral sexual precocity. In women genital bleeding, uterus hypertrophy, high blood pressure and/or abdomen mass may be the only manifestations.
On the biological point, estrogen overproduction with or without increase in other adrenal hormones are the main abnormalities. Radiological examination usually shows the tumor, describes its limits and its eventual metastases. Adrenal and endocrine origins are confirmed by biochemical assessments and histology, but that one is unable to distinguish between benign and malignant tumors, except if metastases are already present. Immunostaining using anti-aromatase antibodies is the only tool that distinguishes FAT from other adrenocortical tumors. Abdominal surgery is the best and the first line treatment. For large tumors (≥10 cm), an open access is preferred to coeliosurgery, but for the small ones, or when the surgeon is experienced, endoscopic surgery seems to give excellent results. Surgery can be preceded by adrenolytic agents such as ortho paraprime dichloro diphenyl dichloroethane (Mitotane), ketoconazole or by aromatase inhibitors, but till now there is not any controlled study to compare the benefit of different drugs. New anti-estrogens can be used too, but their results need to be confirmed in malignant tumors resistant to classical chemotherapy and to conventional radiotherapy. Targeted therapy can be used too, as in other adrenocortical tumors, but the results need to be confirmed.

**Key words:** Adrenocortical tumors, feminization, abdominal surgery, anti-steroid drugs, aromatase inhibitors, targeting therapy

## Introduction

Adrenocortical tumors are relatively frequent in endocrinology. Benign tumors are usually mono secreting and cortisol secretion responsible for Cushing syndrome is the most frequent condition.

Malignant tumors or adrenocortical carcinomas (ACC) are rarer, less secreting, and have a poor prognosis. When they secrete hormones, there is usually a mixed secretion which argues itself for malignancy. In ACC, cortisol secretion is generally prevailing but in some very rare cases androgens, aldosterone or estrogens may prevail. The last condition is very rare and the prognosis is deemed to be the worst. In literature only single cases have been reported in adults[1-25] and in pediatric population.[19,26-41] The largest published series does not exceed two[7,25] and three cases.[10] In our department we recorded five cases but only four have been published.[3,42]

Concerning review of articles, there is only one done by Gabrilov *et al.* before 1970 which collected 52 cases.[43]

To analyze the circumstances of discovery, clinical profile, positive diagnosis, treatment and prognosis we aimed to review all articles published from 1970 to November 2014. The term of feminizing adrenocortical tumors, tumor secreting estrogens were searched in PubMed and Google scholar. But, only relevant and full articles from this search as well as from cross references were retrieved and included. These research helped us to find 49 cases. When we added one of our unpublished case we have totalized 50 cases.

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**Corresponding Author:** Prof. Farida Chentli, Department of Endocrine and Metabolic Diseases, Bab El Oued Teaching Hospital, University of Medicine, Algiers, Algeria. E-mail: Chentli.f@gmail.com

## Definition, Prevalence, Sex Repartition and Age at Diagnosis

Feminizing adrenal tumors (FAT) are defined as adrenal neoplasms with estrogens (estrone and estradiol) overproduction with or without other adrenal hormones.[5,7,10] These exceedingly rare tumors are deemed to have a dire prognosis.[1] They are mainly observed in men or in children, and are exceptional in premenopausal and menopausal women.[15]

Between 1979 and November 2014 we found 41 males among the 50 cases (82%). For adults ($n$ = 33) only two were females. In children there were 10 boys and seven girls. The median age was 42.8 years (19–77) for adults and 5.5 (1.5–14) for children. For Moreno *et al.* FAT account for 0.37% among 801 adrenalectomies.[10]

The main manifestation in men and boys is breast enlargement. Most of FAT are malignant, although some benign cases have been reported.[44] They belong to the vast group of adrenocortical tumors whose prevalence varies from 4 to 12/1,000,000.[45] But, among all adrenal tumors, which are mostly sporadic and exceptionally a part of various family tumor syndromes, FAT account for only 1–2%.[7,10] On another hand 90% of all feminizing tumors are from adrenal origin.[46]

Feminizing adrenal tumors mechanism is still unclear. In published cases no specific mutation has been discovered yet. But, as for all ACC, some authors have discussed a mutation in tumor suppressor genes.[47] Others have identified three main molecular patterns which are: Insulin-like growth factor (IGF)-2, the metabolic pathway Wnt/β-catenin and TP53.1 mutations.[1]

Some ACC are demonstrated to be a part of various family syndromes such as multiple endocrine neoplasia (MEN 1), Carney complex, Beckwith–Wiedemann syndrome, and Li Fraumeni syndrome, others seem to be sporadic.[1]

Concerning FAT, except for one case belonging to MEN 1 syndrome,[1] till now genetic studies failed to demonstrate their real cause. FAT are characterized by an excessive aromatase activity,[29] but sometimes that one is moderate[11] although hyper estrogenism is major.

## Circumstances of Discovery

In feminizing adrenocortical tumors, the main circumstances of discovery are manifestations related to estrogens overproduction, tumor mass[37] or to deterioration of the general condition such as weight loss, strong fatigue, anemia or fever. In some rare cases, a weight gain may attract the attention.

In men the consultation motive was gynecomastia, but some complained from back or abdomen pain, sexual troubles, but rarely from high blood pressure (HBP) with or without heart failure.[4] Women usually complain from postmenopausal genital bleeding[23] or from HBP.[20]

For children, boys consulted for gynecomastia, but rarely for Cushing syndrome complications' such as delirium and aggressive behavior as it was observed in one case.[31] In girls, the main complaint was early breast development ± menstruations. In one case, it was a sub occlusive syndrome.[37]

## Clinical Profile

The main clinical manifestations in men harboring FAT are signs of hypogonadism with or without discrete manifestations of Cushing's syndrome.

Gynecomastia is generally the most important sign observed in males. 98% of men suffering from FAT had gynecomastia.[7,10] Breast enlargement with or without galactorrhea, does not necessarily have an areolar hyper pigmentation. It is usually bilateral and painful.[10] Gynecomastia may be absent at the beginning, when tumor progression is very rapid or when there is a strong deterioration of the general condition.[3] Its size can be mild to moderate, but sometimes it can be very important or even huge looking like a woman's even in boys.

Gynecomastia may be seen with other symptoms secondary to low androgen production such as fatigue, decreased libido and erectile dysfunction.[43] Body hair repartition may remain normal, but shaving frequency might decrease. Testicular atrophy is deemed to be rare on clinical examination.[7,15] But, according to Gabrilove's review, decrease in testes volume was observed in 52%,[43] although a systematic testes echosonography may discover a higher percentage. Sometimes nonspecific signs may be present too. Those are cachexia, fever, anemia, jaundice, and hematuria when the liver and kidneys are involved.[16] Overt clinical features of Cushing's syndrome are rarely observed.

In advanced stages abdomen mass or its metastases may be easily discovered by clinical examination as observed in one of our cases.[3] A moderate or severe HBP with or without pedal edemas maybe observed too.

In children the main symptoms are those of peripheral sexual precocity: Isosexual in girls and heterosexual in boys. In the published cases we analyzed, apart from bilateral breast enlargement in both sexes ± pubic hair, advanced bone age with or without tall stature, and HBP were reported too. Overt Cushing's syndrome[31] is very rare in both sexes and virilizing manifestations although rare may be observed in girls. A palpable mass is relatively rare in children.[37,40]

In women, apart from genital bleeding[23] with or without increased libido, uterus hypertrophy[23] and/or HBP maybe the only manifestations. Hepatomegaly and lower limb edema maybe observed too.[20]

## Positive Diagnosis

Feminizing adrenal tumors positive diagnosis is based on clinical features and hormonal assessment where estrogen secretion is pure or prevailing. Radiological findings and histological aspects are broadly similar to other adrenocortical tumors, except for aromatase immuno-staining which is positive in the pathologic tissue secreting estrogens.[2]

### Clinical features

On clinical examination as it was aforesaid gynecomastia is the most important abnormality in men. Breast development is related to high estrogens/testosterone ratio which is usually ≤1/100 in healthy men. This ratio rises up to 1/8.5 in tumors with estrogens' overproduction.[16]

Other features which can be observed in FAT are those related to hypogonadism manifestations such as testicular hypotrophy, partial or total loss of scrotum folds and pigmentation, and body hair rarefaction. HBP, although very rare, maybe observed even in children.

When the adrenal tumor is small, abdominal examination is generally unremarkable. But, when the neoformation is large it can be palpable. A huge tumor can even distort the abdominal wall as we observed it. In these cases an embossed liver and subcutaneous or parietal nodules may be present reflecting metastases.[3]

### Biological assessment

Biological assessment shows estrogens overproduction, with or without other adrenocortical hormones with normal or low gonadotropins. In adults population, estradiol production is generally pure, but in some cases a sub clinical or overt Cushing syndrome may be present. In women androgens excess can be observed too. The mixed secretion is apparently prevailing in children.

Hyper estrogenism may be a result of a dual source: Over production by the tumor (proved by adrenal venous blood samples) and peripheral androgens' conversion to estrogens in the adipose tissue.[14]

Estrogens secretion by FAT may remain dependent on pituitary adrenocorticotropic hormone activity for a long time which explains that tumors secreting estrogens may be hampered by dexamethasone administration.[15]

Estrogens' overproduction results from an increase in aromatase activity in the adrenal tissue as demonstrated by Moreno *et al*.[10] These authors have proved that *in vitro* aromatase activity is higher in tissues obtained from FAT than in normal adults' adrenal tissues. So, excessive androgens transformation to estrogens leads to an increase in estrogens/androgens ratio responsible for gynecomastia and other hypogonadism features and inhibition of the hypothalamic-pituitary-gonadal axis inducing a lack of luteinizing hormone-releasing hormone pulsatility and low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion.[10,11,29,48]

Apart from plasma or urinary cortisol, aldosterone may be increased too. Increase in some precursors such as progesterone, 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, D4androstenedione (D4A), dehydroepiandrosterone (DHEA) and DHEA sulfate plead for malignancy as in other adrenal tumors. Increase in precursors is explained by an acquired deficiency in adrenal enzymes such as 21-hydroxylase, 11-hydroxylase, or 3-beta-hydroxysteroid dehydrogenase.[15]

Decrease in testosterone observed in the majority of adult males is probably due to several mechanisms. The first one is the inhibition of FSH and LH secretion and pulsatility due to high concentrations of estrogens at the hypothalamic level.[10,12] The second mechanism can be explained by leydig's cells inhibition secondary to estrogens high concentrations.[10] The third one is related to an increase in sex hormone binding globulin (SHBG) secondary to estrogens excess too. As SHBG has a great affinity for testosterone, the consequence will be a decrease in free testosterone with hypogonadism exaggeration.[15]

High blood pressure is related to an increase in renin precursors' synthesis by the liver. As a result, angiotensin I is converted to angiotensin II leading to aldosterone high concentrations.[15] In rare cases, it can be a result of aldosterone high secretion by the tumor itself.

Heart troubles, especially cardiac insufficiency with or without ventricular tachycardia are related to massive

estrogens concentration while physiological concentrations are usually cardio-protective.[4]

### Radiological findings

Radiological signs are important to consider although they are not specific of tumors secreting estrogens. As in other adrenal tumors, plain radiographs, excretory urography and nephrotomograms were used in the past to show an abdominal mass compressing or displacing the kidney. Echosonography which is a noninvasive exploration is replacing old explorations as it usually shows the tumor in the supra renal area and demonstrates or not kidney and/or other adjacent organs involvement. Lymph nodes and/or liver metastases can also be shown by echosonography which can also demonstrate vena cava thrombosis. Computed tomography (CT) shows the tumor and provides guidance for malignancy such as: Tumor size ≥6 cm, inhomogeneous aspect and poor limited margins, spontaneous density >10 Hounsfield units, intense enhancement of the tumor after injection, large areas of necrosis and/or micro-calcifications, and compression of adjacent organs. CT scan can help for fine nodule aspiration too in order to prove the diagnosis as in one of our case, and to confirm estrogen secretion by immunostaining. The positron emission tomography (PET) scan could help too for a precocious diagnosis of the adrenal tumor and its metastases especially when other explorations fail to show the adrenal tumor.

### Pathological aspect

Histology proves the endocrine and adrenal origins, but cannot distinguish benign from malignant tumors except when metastases are present. Positivity for melan A and synaptophysin antibodies usually could not distinguish between different types of adrenocortical tumors, but a strong positivity of aromatase immunostaining confirms estrogen secretion in the tumor tissue.[14]

### Macroscopic aspect

As any other adrenocortical carcinoma, FAT is a large, round, encapsulated, yellow or greyish-orange tumor, with areas of necrosis and hemorrhage.[10] A large size and large areas of necrosis plead for malignancy. To the best of our knowledge the hugest adrenocortical tumor secreting estrogens weighed 10 kg.[10]

### Microscopic aspect

On histological aspect some features argue for malignancy, but none of them is an absolute criteria. Indeed, Melero *et al*. reported a case considered as histologically benign, that recurred and presented peritoneal metastases refractory to medical treatment 3 years after a total resection.[49]

The Weiss score, which is applicable to all adrenocortical tumors, pleads for malignancy if >3.[50] In the literature review we did, this score varied between 3 and 8.

Weiss's score is based on: Abnormal mitosis with high mitotic index, depletion of light cells (<25%), diffuse architecture (>33%), important necrosis, and invasions of the tumor's capsule, veins or sinusoids. Each abnormality is scored 1 with a maximum of 9 points.

Aubert *et al*. have modified this score by awarding two points for a high mitotic index or when light cells are <25%.[51]

Some authors prefer the Fuhrman's index that takes into account monstrous cells and abnormal nuclei and nucleoli: More the nuclei are large and irregular, more monstrous cells are numerous, the higher is the index of malignancy.

Proliferative indexes such as Ki 67 are also interesting to consider. The Ki 67 is significantly higher in ACC than in adenomas. A Ki 67 <2.5% pleads for a benign tumor. However if it is above 10%, it argues for a malignant one. Intermediate values plead for malignancy too[52] although this is not specific of FAT. Invasion of adjacent structures argues for malignancy too.

When the tumor is malignant, metastases are frequent. As in other malignant adrenal tumors metastases can be found in the mesenteric lymph nodes, the peritoneum, the pancreas, the liver, the kidney, the spleen[52,53] and even in the small intestine.[3] Parietal and/or skin metastases are rare. Bone and cerebral localizations are also possible at the end stage of the disease.

## Extension of the Tumor

Work up for local (adrenal area and ganglia) and distant diffusion of the tumor is mandatory.

Abdomen and thoracic CT scans, bone scintigraphy, cerebral magnetic resonance imaging (MRI) and even the PET scan are necessary to seek metastases especially in the peritoneum, the liver, the pulmonary and pleural areas, but also in bones and in the brain in order to classify the tumor.

Different classifications were proposed for all adrenal tumors. In 2004, the most important one was the World Health Organization classification based on the criteria proposed by the international organization against cancer. In 2008, European Network for the Study of Adrenal Tumors proposed another classification, but all of them derived from the Mac Farlane's, and aimed to give a prognosis staging.[48]

Adrenal tumors in general are classified in four stages and grades according to their size: Stage 1 ≤ 5 cm, stage 2 > 5 cm, stage T3 with an infiltration of the surrounding tissues, and stage T4 corresponds to a tumor invading adjacent organs or with venous thrombosis.

To these classifications was added the tumor, lymph nodes, and metastases (TNM) classification that takes into account lymph nodes invasion and distant metastases. The tumor is classified N0, M0 if there is not any lymph node metastasis or visceral localization. In contrast the tumor is classified N1, M1 if lymph nodes and distant metastases are present.

## Treatment

Feminizing adrenal tumors management is similar to the one of other adrenal tumors, except for small differences.

### Main rules

According to the extreme rarity of FAT and a lack of specific data in terms of specific treatment, many researchers agree to apply for the procedure already used for other adrenocortical tumors. So surgery preceded or not by chemotherapy, is considered as the best treatment. Any adrenal secreting mass should be removed, independently of its size, especially if it is a feminizing one. Work up for pheochromocytoma and hyper cortisolism is mandatory.[15] When metastases are present, the National Comprehensive Cancer Network recommends surgical resection of at least 90% of the tumor.[15] If not, the recurrence will be rapid. Chemotherapy should be done before and after surgery if possible when the tumor seems malignant from the first exploration. Treatments which are available now are: Surgery, medication and radiotherapy.

### Surgery

Surgery was and remains the cornerstone for FAT treatment as in other adrenal tumors.[45,46]

The aim of surgery is to extract the tumor in a mono bloc which sometimes requires removal of a portion or total adjacent organs such as kidney, spleen, liver, pancreas and colon. The dissection should be systematic.[45,47] and the patient's prognosis depends on the experience and ability of the surgeon.[45]

When malignancy is suspected, the open surgery seems the most appropriate, as the tumor can be best exposed. The open surgery also helps to prevent tumor dissemination by preserving the integrity of the capsule. Some authors consider thrombosis in the inferior vena cava or in renal vein should not be a contraindication for surgery.[47]

As for other kind of adrenocortical tumors, the laparoscopic surgery is still a matter of controversy. For some authors, laparoscopic surgery is good, especially for someone who masters it very well. However, the current consensus favors traditional surgery when the adrenal tumor has invaded adjacent organs, when there are regional lymph nodes metastases, or when the tumor is >10 cm.[47]

Although laparoscopic surgery is currently the gold standard for benign adrenal lesions, a retrospective study has shown a higher frequency of local recurrence and a higher risk of capsular rupture and tumor dissemination due to pneumoperitoneum.[47] On another hand, a German study which analyzed a large number of adrenal tumors did not demonstrate inferiority of laparoscopy for tumors whose size is <10 cm compared to conventional surgery.[54]

However, most authors emphasize the need for a broad oncologic resection including complete block resection of the tumor and if necessary a portion of adjacent tissues with lymph nodes dissection,[10,55] because some authors still think adjacent organ invasion and tumor larger than 6 cm should remain contraindications for laparoscopic surgery.[56] In the cases published after 1970, most FAT had an open surgery.

### Medical treatment

Medical treatment is indicated for advanced stages of adrenocortical tumor regardless of the type of secretion.[45] Many products have been tried such as mitotane, ketoconazole, aromatase inhibitors, and classical chemotherapy. But, till now there are no well controlled studies to compare the benefit of different drugs as first line therapy or as adjuvant therapy.

#### *Mitotane or ortho paraprime dichloro diphenyl dichloroethane*

This product is the most used as it inhibits hormonal secretion and has a cytolytic or adrenolytic power.

Apart from its adrenolytic action, mitotane acts by inducing formation of free radicals that block adrenal steroidogenesis by inhibiting 11 β hydroxylase that is why it is interesting in FAT.[45,47,52]

#### *Ketoconazole*

Ketoconazole may be used in fat too[17] especially when there is a mixed secretion including cortisol. It should not be used in a patient with HBP, because it may increase 11-deoxycorticosterone.

#### *Aromatase inhibitors*

Aromatase inhibitors are enzymes that inhibit androgens conversion to estradiol. That is why they are useful in FAT.

Many authors have discussed the efficacy of different generations of aromatase inhibitors, but it was concluded that only aminoglutethimide is interesting among the old products.

Newer aromatase inhibitors such as formestan, anastrozole, letrozole, mainly used in gynecomastia of nonadrenal origin, may be used in FAT, but their efficiency is to demonstrate.

Aminoglutethimide that blocks cortisol, aldosterone and androgens synthesis also inhibits peripheral aromatization of androgens to estrogens.[45] It can therefore be used as a complementary treatment for FAT when surgical removal is partial, or when there is an estrogens' residual secretion. Similar to ortho paraprime dichloro diphenyl dichloroethane (Op' DDD), aminoglutethimide is an adrenolytic too,[53,54] so glucocorticoids' replacement is mandatory.[53]

For the cytolytic action, *in vitro* studies showed that aminoglutethimide inhibits tumor cell proliferation,[44] but in clinical practice some authors use it just as an adjuvant or a palliative treatment for advanced metastatic tumors.[53,55]

### *Conventional chemotherapy*

Conventional chemotherapy is also used for high grade tumors and for tumors resistant to op' DDD or to aminoglutethimide.[56] The most used diet is the one using cisplatin, etoposide, and doxorubicin, but according to our modest experience and to literature review the result is very modest or even poor.

### *Targeted chemotherapy*

Target therapy using epidermal growth factor inhibitors, anti-angiogenic agents, IGF inhibitors, and fibroblast growth factors inhibitors may be tried in tumors with advanced stage or resistant to classical chemotherapy in order to improve survival and/or patient's comfort.

### *Radiotherapy*

Conventional radiotherapy can be used in FAT at least as a palliative treatment for symptomatic metastases involving bones. Biphosphonates may be used too. Both radiotherapy and biphosphonates would prevent fractures and nerves' compression. For some authors, radiotherapy with or without chemotherapy, may be useful in partially removed adrenocortical tumors, independently of their secretion. They may reduce tumor size and/or recurrence.[45,56-61] But, it seems this therapeutic association did not impact on overall survival.[61] In the 50 last published cases, only few persons had radiotherapy in addition to chemotherapy, therefore it is difficult to make an objective conclusion about its efficacy in FAT.

## Monitoring and Follow-up

In terms of adrenocortical tumors, postoperative adrenal exploration is mandatory for the diagnosis of adrenal insufficiency especially when there is a mixed secretion. Estrogens assessment is also necessary to ensure complete resection of the tumor secreting estrogens.

Endocrine exploration seeking recurrence is recommended every 3 months (especially E2, but also: Cortisol before and under dexamethasone, 17-OHP, DHEAS, D4A, and testosterone). Chest and abdominal CT scans are needed every 3 months the first 2 years, then at least every 6 months for 5 years if patients are still alive. After 5 years (which is a quite rare situation for FAT) an annual exploration is recommended.[55,62] Brain MRI and bone scintigraphy are sometimes needed in advanced tumors, but in FAT brain and bone metastases are generally preceded by an increase and/or exaggeration of estrogens secretion.

## Prognosis

Feminizing adrenal tumors are tumors with a dire prognosis. For Lanigan *et al.* the median survival was 2.9 months after diagnosis.[16] In our own experience, the survival lasted 4 years in one of our patient with diffuse metastases, Moreno *et al.* reported a survival of 7 years[10] and a pediatric case died from his metastases after 12 years.

Some authors consider adrenal tumors secreting estrogens are immediately suspicious or straight away malignant whatever their presentation and size are.[63] However, some features such as mixed secretion, very high initial level of estradiol, and a large tumor are of bad omen.[10]

In postoperative period, lack of hormonal normalization, or a relapsing tumor predict a poor prognosis too.

## Conclusion

Feminizing adrenocortical tumors or adrenal tumors secreting estrogens are extremely rare. They are mostly observed in men and children in whom the main symptoms are breasts enlargement.

Their diagnosis is based mainly on estrogens assessment. But, a mixed secretion, presence of adrenal precursors and a large tumor size argue for malignancy. The treatment should be based on surgery plus op' DDD or aromatase inhibitors with or without standard or targeting chemotherapy. The prognosis depends on the stage of the tumor at diagnosis and on the progression of the disease, but in general the

final prognosis is tremendously poor especially for adults in whom benign tumors are quite exceptional.

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