ORIGINAL ARTICLE

Feminizing Adrenocortical Tumors as a Rare Etiology of Isosexual/Contrasexual Pseudopuberty

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What is already known on this topic?

Feminizing adrenocortical tumors (FATs) are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia. While boys present with contrasexual pseudopuberty signs, girls present with isosexual pseudopuberty.

What this study adds?

FATs are more common in children ≤8 years of age, with a median age at diagnosis of six years. FATs are usually malignant in adults whereas in children approximately half of the FATs are benign. In children the assessment of malignant potential depends on clinical behavior of the tumor. Although complete surgical resection of benign FATs is thought to be curative, long-term follow-up is required because of the unpredictability of these tumors. FATs occurring in childhood may carry a better prognosis than in adult males because most of the FATs in children did not recur during follow-up since diagnosis is made early, as typical presenting signs are more obvious before puberty.

Abstract

Objective: Estrogen-secreting adrenocortical tumors (ACTs) are quite rare with feminizing adrenocortical tumors (FATs) accounting for 0.37-2 % of all ACTs. The aim was to evaluate clinical and hormonal characteristics of FATS as well as treatment options and follow-up in the pediatric age group.

Methods: Medical records of children with ACTs presenting to a single center in the last two decades were reviewed. Literature review within Pubmed revealed 34 pediatric patients (22 boys) with FAT among 192 articles.

Results: Among the 25 children presenting with ACTs in the last two decades, two new pediatric cases of FAT were identified, one benign and the other malignant, in two genders with different clinical presentations. Literature review showed that FATs are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia. FATs are more common in children ≤8 years of age, with a median age at diagnosis of six years. While boys present with contrasexual pseudopuberty signs, girls present with isosexual pseudopuberty. A high estrogen level strongly supports diagnosis, while elevations in other adrenal hormones may be seen. FATs are usually malignant in adults and prognosis is generally very poor. However, in children approximately half are benign although assessment of malignant potential depends on clinical behavior of the tumor. FATs are very unpredictable so even after surgery long-term follow-up is required. FATs presenting in childhood may have a better prognosis than adult presentation tumors as most FATs in children are followed without recurrence of tumor.

Conclusion: FATs are more common in children ≤8 years of age, with a median age at diagnosis of six years. FATs in childhood may have a better prognosis than in adult males.

Keywords: Adrenal adenoma, adrenal tumor, adrenocortical carcinoma, adrenocortical tumors, childhood, children, children and adolescents, estrogen

Introduction

Adrenocortical tumors (ACTs) are rare in childhood, accounting for less than 0.2% of childhood malignancies, but nearly 6% of adrenal tumors (1). Childhood ACTs are usually functional tumors; the rate of being hormonally active is 90% in children compared to 50% in adult cases (2,3). While adults usually have single hormone secretion, children often have multiple hormone secretion. Complete hormonal workup of ACTs revealed the predominance of mixed hormone-secreting types of tumor although some cases lack the appropriate clinical findings. Hormonal work-up of these tumors showed that half of the patient population had tumors secreting a combination of androgens and cortisol, whereas almost one third had ACTs secreting androgens alone (4). The clinical presentation depends on the hormones secreted by the tumor. The most common presenting symptoms are virilization due to androgen secretion, followed by Cushing's syndrome due to cortisol secretion and then hyperaldosteronism (3,4,5,6). Estrogen-secreting ACTs are quite rare, feminizing adrenocortical tumors (FATs) accounting for 0.37-2% of all ACTs (7). FATs may secrete estrogen (estrone and estradiol) alone or in combination with other adrenal hormones and are more prevalent in adult males, are usually malignant and have a poor prognosis (7).

The clinical manifestations of FATs include feminizing symptoms of excessive estrogen production, symptoms due to compression by the tumor mass, or constitutional symptoms such as weight loss and fatigue. Girls usually present with precocious puberty (isosexual pseudopuberty), while boys present with bilateral gynecomastia (contrasexual pseudopuberty) and delayed puberty. In boys gynecomastia is the most common symptom of a FAT with a rate of 98% (8). Diagnosis of FATs depends on the clinical signs and hormonal analysis. Hormone profiles show overproduction of estrogen alone or in combination with other adrenocortical hormones, alongside normal or low gonadotropin levels (9,10). Radiological and histological findings are similar to those of other ACTs. Histopathology examination normally shows positive immunostaining for aromatase in the tumor tissue (11).

In this study the aim was to evaluate the clinical and hormonal characteristics, treatment options and outcome in FATs occurring in the pediatric age group. For this purpose the medical records of children with an ACT followed in our unit in the last two decades were reviewed with the intention of detailed evaluation of the clinical and hormonal characteristics, treatment methods and outcomes of the patients who were diagnosed with FAT during this period. A systematic literature review was performed and the features of similar published pediatric cases were analyzed. We wished to highlight this rare tumor and draw attention to the variety of FAT characteristics by presenting the cases with FAT followed-up in our unit and by reviewing the published cases with FAT in childhood period.

Methods

The medical records of children with ACT who were followed up between 1999 and 2020 in the pediatric endocrinology unit at Hacettepe University İhsan Doğramacı Children's Hospital, Ankara, were reviewed retrospectively. Data regarding age, sex, presenting symptoms, clinical characteristics, laboratory investigations including hormonal analysis, imaging techniques including ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging, histopathological reports, treatment and outcomes were extracted from the medical files. Cases with FAT were identified from amongst all the ACTs followed up in our unit. Cases with FAT were described in detail. A systematic literature review was also performed. A search was made using PubMed/MEDLINE using the following keywords: "Feminizing adrenocortical tumor" and "Feminizing adrenal tumor" and was filtered for articles published in English and Turkish. The literature was queried from inception to December 1, 2020. We included all articles that reported children who had FATs. The following parameters were collected from included studies: age at diagnosis, gender, clinical presentation, hormonal evaluation, treatment options, clinical course of the tumor, and survival/follow-up period.

Statistical Analysis

Data analyses were performed by using Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data were described as mean ± standard deviation (SD) and categorical data were described as the number of cases (%). Differences between two independent groups were compared by Student's t-test while differences between more than two independent groups were analyzed by one-way ANOVA. A $p < 0.05$ was considered to indicate statistical significance.

Results

A total of 25 patients with ACT had been followed up in our pediatric endocrinology unit during the study period. Since histological criteria to differentiate malignant behavior in childhood ACTS are not reliable, all lesions were categorized as ACT instead of adenoma or carcinoma. By this classification two patients had FAT and the other twenty-three patients had ACT. The clinical, hormonal and pathological characteristics of the cases with ACT are given

in a recently written article by Ardicli et al (12). Clinical, hormonal, pathological evaluations as well as management and outcome of the patients with FAT are given below in detail.

Case 1

A 13.5-year-old boy presented with bilateral breast enlargement and weight gain for the last four months. No discharge from the breasts was noted. He did not have headache, nausea or vomiting, flushing, palpitation, sweating or diarrhea. He was not using any medication. His family history was unremarkable. On physical examination body weight was 61.4 kg [1.1 SD score (SDS)], height was 156.4 cm (-0.5 SDS), body mass index was 25.1 kg/m^2 (1.6 SDS), heart rate was 90/min and blood pressure was 140/85 mmHg. He had a cushingoid appearance with purple striae, buffalo hump, moon face and centipetal fat accumulation. He had bilateral, Tanner stage 4 gynecomastia with Tanner stage 4 pubic hair, testis volumes of 6/8 mL, and stretched penile length of 7.5 cm. Laboratory examination showed that he had hyperestrogenism, hyperandrogenism and hypercortisolism (Table 1). Abdominal USG showed a 102x94 mm, round, hypoechoic mass with echogenic septates and increased blood flow at the right adrenal lodge. A hypoechoic, thrombotic mass markedly occluded the lumen of the inferior vena cava (IVC). Abdominal CT showed the mass was exerting pressure on the right kidney and the right lobe of the liver. A chest CT revealed pulmonary metastasis. Antithrombotic treatment (enoxaparin sodium) was administered for the thrombus in the IVC. Amlodipine

was started for hypertension. The mass with right adrenal gland and tumor thrombus were resected under steroid coverage. Histopathological examination confirmed the diagnosis of adrenocortical carcinoma with high mitoses, sinusoidal and venal invasions and penetration of the capsule of the adrenal gland. Hormone levels declined in the postoperative period. The patient was administered a chemotherapy protocol, including cisplatin, etoposide and doxorubicin. Hydrocortisone replacement at maintenance dose was given along with mitotane treatment, and the dose was adjusted with respect to the patient's clinical findings. The patient was monitored for blood pressure, serum potassium, plasma renin and aldosterone levels to check for a possible mineralocorticoid deficiency, though no such deficiency was found during follow-up. As the patient received mitotane, thyroid function tests were closely monitored and remained normal.

While a successful decline was observed in the hormonal secretion and gynecomastia post-surgery, the patient again developed gynecomastia accompanied by a huge elevation of testosterone (T), adrenal androgen (androstenedione) and estradiol levels following commencement of mitotane. Since the imaging studies did not show a relapse or recurrence, elevated T was attributed to the inhibition of 5-α-reductase enzyme activity due to mitotane therapy. This suggestion was confirmed by an elevated T/dihidrotestosterone (DHT) ratio of 38.5 (T: 1374.17 ng/dL, DHT: 357.12 pg/mL) (13). Serial measurements of T and androstenedione revealed a gradual decline in the hormone levels after the cessation of mitotane treatment. During the three-and-a-half year follow

Table 1. Pre-op and post-op laboratory examinations of the cases

Name of the hormone	Case 1 Pre-op	Case 1 Post-op	Case 2 Pre-op	Case 2 Post-op	Normal values
FSH (IU/L)	< 0.3	2.94	0.66	4.6	0.7-18
LH (IU/L)	0.27	1.74	< 0.2	0.3	2.4-10
Testosterone (ng/dL)	151.01	14.8	116	< 20	< 20 (prepubertal), 39-631 (pubertal in boys)
E$_2$ (pg/mL)	129.37	11.82	275	< 20	< 10
08.00 ACTH (pg/mL)	< 5.0	22.3	19	25	0-46
08.00 cortisol (μg/dL)	10.47	10.26	6.5	11.6	6.7-22.6
23.00 ACTH (pg/mL)	< 5.0				0-30
23.00 cortisol (μg/dL)	10.2				3-16.6
24 hour urinary cortisol (μg/day)	N/A*				2.6-37
17-OH progesterone (ng/mL)	5.66	1.11	1.2	0.42	0.59-3.44
11-deoxycortisol (ng/mL)	116.16	4.55	3.4	3.2	< 7.2
Androstenedione (ng/mL)	> 10.0	0.66	4.1	0.36	< 0.51 (prepubertal), 0.31-2.4 (pubertal)
DHEA-SO$_4$ (μg/dL)	415.26	47.1	> 1000	< 30	< 35 (prepubertal), 35-430 (pubertal)
Na (mEq/L)	139	136	138	140	135-145
K (mEq/L)	4.2	4.3	4.3	4.4	3.4-4.7
Cl (mEq/L)	103	101	105	107	101-109
Renin (pg/mL)	33.2	18.6	28.1	N/A	2.7-16.5 (supine), 5.41-34.53 (standing)
Aldosterone (pg/mL)	77.0	82.4	82.6	N/A	10-160 (supine), 35-300 (standing)

*N/A: not available, FSH: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, DHEA: dehydroepiandrosterone

up there were no further clinical symptoms and radiological finding did not indicate recurrence of the tumor.

Case 2

A 7-year-old girl presented with bilateral breast development and appearance of pubic hair which had been present for the last six months. She was not using any medication and her family history was unremarkable. On physical examination she had bilateral Tanner stage 3 breast development with Tanner stage 3 pubic hair. Laboratory examination revealed elevated estradiol and androgen levels with suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Table 1). Abdominal ultrasound showed a 65x53 mm, round, hypoechoic, heterogeneous mass with clear boundaries at the left adrenal lodge with a uterus of

pubertal size and pre-pubertal sized ovaries. An abdominal CT indicated mass pressure affecting the left kidney. The mass, together with the left adrenal gland was resected. Histopathological examination confirmed the diagnosis of ACT. Hormone levels declined in the postoperative period. The patient was followed until the age of 20 years and during this time she had neither clinical symptoms nor radiological findings indicating recurrence of the tumor. Thus there was 13 years of disease-free survival.

Literature Review

There were 34 pediatric FAT cases that have been described among 192 articles identified from the PubMed database (Table 2). The first pediatric case was a 4.6-year-old male described in 1948 (14). Twenty-two of the cases (65%) were

Table 2. Feminizing adrenocortical tumors in the pediatric age group

First author (reference number)	Age (years)	Gender	Clinical findings at presentation	Hormonal evaluation (Increased hormone levels)	Treatment	Clinical course of the tumor	Survival/Follow-up
Wilkins (14)	4.7	Boy	Bilateral gynecomastia	Estrogens, 17 ketosteroids	Surgery	Benign	No recurrence in 4 year of follow-up, alive after 14 years
Fontaine et al (30)	5	Boy	Bilateral gynecomastia	Estrogens, 17 ketosteroids	Surgery	Malignant with vascular spread	No recurrence 7 years later, alive after 10 years
Snaith (25)	5.5	Girl	Breast development, pubic hair, vaginal bleeding	Urinary estrone, estradiol, estriol, 17 ketosteroids	Surgery	Anaplastic changes (malignant?)	Alive and well after 8 years
Mosier and Goodwin (31)	7	Boy	Gynecomastia, accelerated linear growth	Estrogens, 17 ketosteroids	Surgery	Benign	2 year follow-up, no recurrence, alive after 4 years
Peluffo (17)	6.7	Girl	Breast development, axillary and pubic hair, vaginal bleeding, painful abdominal mass	N/A	Surgery	Malignant	N/A
Ferrante et al (65)	2.2	Girl	Breast enlargement, pubic hair, hypertrophy of labia minora, advanced bone age	N/A	Surgery	Malignant	N/A
Wilkins (66)	3	Girl	Vaginal bleeding, breast development, accelerated bone age, pubic hair	Estrogens, 17 ketosteroids in 24 hour urine	Surgery	Benign	3 years no recurrence
Bacon and Lowrey (18)	6	Boy	Gynecomastia; acne, pubic hair Palpable tumor	Estrogens, 17-ketosteroids	Surgery	Originally benign, at follow up malignant (adenoma with neoplastic thrombus)	He was alive, well and free of metastases for 7.5 years, then died of disseminated metastasis 8 yrs after operation; 9 yrs. after disease onset.
Halmi and Lascari (20)	4	Girl	Signs of virilization, hypercortisolism, hyperestrogenism	Urinary 17-ketosteroids, 17-hydroxycorticoids, Urinary DHEA	Surgery op'DDD	Malignant	Recurrence of tumor and metastases to lungs and liver Died 3 years after the onset of disease

Table 2. Continued

First author (reference number)	Age (years)	Gender	Clinical findings at presentation	Hormonal evaluation (Increased hormone levels)	Treatment	Clinical course of the tumor	Survival/Follow-up
Castleman et al (27)	6.8	Boy	Gynecomastia, pubic and axillary hair deveopment, grow rapidly	Elevated urinary 17-ketosteroid	Surgery	Malignant with pulmonary metastases	Died on operating table
Leditschke and Arden (19)	5	Boy	Bilateral gynaecomastia (no pain, no discharge from the nipples), advanced bone age, increased appetite, pubic and axillary hair development, palpable tumor	Elevated urinary 17-ketosteroid and 17-hydroxyketosteroid, and urinary estrogens	Surgery	Benign (From the pathological evidence it was unable to predict how the tumor will behave)	No recurrence 1 year post excision
Bhettay and Bonnici (10)	6	Boy	Bilateral gynecomastia	Urinary estrogens	Surgery	Benign	3 years later no signs of recurrence
Howard et al (32)	N/A	Boy	Bilateral gynecomastia	Elevated estrogen levels but normal levels of 17-ketosteroids	Surgery	Benign	N/A
Visconti et al (16)	3.7	Girl	Left abdominal mass, weight loss, irritability, high blood pressure	24 hour urinary 17-hydroxy- and 21-oxosteroids	Surgery, Chemotherapy	Malignant	No recurrences in 39 months
Sultan et al (33)	15	Boy	Bilateral gynecomastia, prepubertal sized testes, pubic hair was present	Estradiol (urine and plasma) urinary 17-hydroxysteroids slightly increased	Surgery	Benign	2 year follow-up no recurrence
Wohltmann et al (24)	1.8	Girl	Breast development, clitoral enlargement, and an estrogenized vagina, pubic hair	Estradiol, DHEA-SO$_4$	Surgery	Capsular invasion (malignant?)	Patient is healthy over 10 years later
Drop et al (34)	6.5	Girl	Breast development, pubic and axillary hair	Estradiol, testosterone, 11 deoxycortisol, 17-OH-progesterone, DHEA, DHEA-SO$_4$, androstenedione	Surgery, Radiotherapy	Malignant	No recurrence after 1 year
Itami et al (35)	6	Boy	Bilateral gynecomastia, axillary and pubic hair, penile size enlargement	Estrone, estradiol, testosterone, androstenedione, 11-deoxycortisol	Surgery	Benign	N/A
Comite et al (23)	2.8	Girl	Breast and pubic hair development	Estradiol, estrone, DHEA, DHEA-SO$_4$, androsteneione, testosterone	Surgery	Potentially malignant (Extension of the tumor into the capsule)	No recurrence 1 year after surgery
Telander et al (36)	N/A	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	N/A
Desai and Kapadia (42)	8	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	N/A
McKenna et al (15)	6	Girl	Virilization	Estradiol, DHEA-SO$_4$, testosterone, androstenedione	Surgery	Malignant	Recurrence and died 16 months after presentation
Bass and Sochett (37)	7	Boy	Bilateral gynecomastia, and rapid growth over the preceding six months	Estradiol elevated DHEA-S, androstenedione, 11-deoxycortisol mildly increased	Surgery	Benign	No recurrence in 6 months
Ghazi et al (21)	14	Boy	Gynecomastia, facial edema, striae, hypertension, delirium, features of Cushing syndrome	Estrogen, cortisol, 24 hour urinary 17-hydroxysteroids	Surgery Bilateral mastectomy	Malignant? (tumor > 100 gr and 6 cm in size)	No recurrence after one year

Table 2. Continued

First author (reference number)	Age (years)	Gender	Clinical findings at presentation	Hormonal evaluation (Increased hormone levels)	Treatment	Clinical course of the tumor	Survival/Follow-up
Watanabe et al (38)	1.5	Boy	Bilateral gynecomastia, pubic hair, penile size enlargement	Estradiol, testosterone DHEA-S	Surgery, mitotane	Malignant	No recurrence in 6 months
Phornphutkul et al (57)	7.8	Girl	Isosexual precocious puberty, breast development at 7.75 years old, menarche at 8.75 years old, pubic hair development	Estradiol, estrone, DHEA-S, increased 17-ketosteroids, estrone, estradiol, and estriol in 24 hour urine analysis, No suppression in cortisol levels in dexamethasone suppression tests	Surgery	Benign	No residue or recurrence in the first year following surgery
Hsiao et al (29)	2.2	Boy	Bilateral gynecomastia, pubic hair development	Estradiol, testosterone	Surgery	Benign	5 years later no recurrence
Bouyahia et al (28)	5	Girl	Isosexual precocious puberty (breast development, menarche, pubic hair deveopment	Estradiol, testosterone	Surgery	Benign	After a follow-up of 6 years, patient has not had any relapse or metastasis
Bawri et al (22)	18	Boy	Bilateral gynecomastia, striae over axilla, and breast, thigh, and facial puffiness for 4 years, Cushingoid appearance Dull, vague abdominal pain localized to the right upper quadrant	Cortisol, DHEA-SO$_4$	Surgery	Malignant	The patient is alive with no metastases 1 year after surgery
Sindgikar et al (39)	6	Boy	Bilateral gynecomastia	Estradiol	Surgery, chemotherapy (cisplatin, etoposide)	Malignant with micrometastasis	N/A
Angotti et al (26)	7	Boy	Bilateral gynecomastia, increased somatic growth	Estradiol	Surgery	Low risk of malignancy	N/A (1 month following surgery patient was well)
Soliman et al (67)	6	Boy	Bilateral gynecomastia and breast tenderness	Estradiol	Surgery	Benign	N/A
Guidoni et al (68)	7.5	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	No recurrence after 1 year
Takeuchi et al (40)	4.7	Boy	Bilateral gynecomastia, growth spurt, no sign of virilization	Low LH/FSH levels and elevated estradiol/testosterone levels, Elevated estradiol, testosterone, DHEA-SO$_4$, androstenedione high percentage of urinary estrogen metabolites	Surgery	Malignant	No relapse after 2 years An investigation for *TP53* gene aberrations revealed the presence of a germline point mutation in exon 4 [c.215C > G (p.Pro72Arg)]
Patients presented in this report	13.5 7	Boy Girl	Bilateral gynecomastia, cushingoid appearance, hypertension Breast development, vaginal bleeding	Estradiol, androgens, cortisol Estradiol, DHEA-SO$_4$	Surgery Surgery	Malignant (metastatic) Benign	Alive with no recurrence for 3.5 years Alive with no recurrence for 13 years

N/A: not available, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEA: dehydroepiandrosterone, yrs: years

boys and 12 of them were girls, giving a male to female ratio of 1.8:1 (22/12). The age at diagnosis of the cases ranged between 1.5 and 18 years with a median age of six years old. The age of diagnosis of two cases was not specified. While the age of diagnosis of 21.9% (7/32) of the remaining 32 cases was < 4 years, 65.6% (21/32) of them were 4-8 years old, and 12.5% (4/32) were ≥8 years of age at diagnosis. All 22 boys had bilateral gynecomastia at the time of diagnosis. Penile enlargement with pre-pubertal volume testes were also reported in boys. In girls, breast development was present in all except two cases, while vaginal bleeding was reported in five cases. In the two girls without breast development, one exhibited virilization (15), and the other case was admitted at the age of 3.7 due to weight loss, irritability, and high blood pressure while a left abdominal mass was detectable by palpation on physical examination (16). In addition, abdominal mass was palpated during examination of two boys of five and six years old and a girl of 6.7 years old (17,18,19). Besides typical findings of virilization (pubic and axillary hair), acne, accelerated linear growth and advanced bone age were also observed in both genders. Features of Cushing syndrome, including facial edema, striae over the body, hypertension, and delirium were reported in two girls aged 3.7 and four years and two boys aged 14 and 18 years (16,20,21,22). Isolated estrogen secretion was reported in eight boys (23.5%, 8/34) aged between 6-8 years. All other cases had mixed hormone secretion. While androgen and estrogen secretions were seen together most frequently (61.8%, 21/34), in five cases these secretions were accompanied by excess cortisol (14.7%, 5/34).

Masses were surgically removed in all cases. Of the 34 cases, 16 (47.1%) were benign, and 12 (35.3%) were malignant, based on histological reports. In five cases (14.7%), a distinction between benign/malignant could not be made histologically (21,23,24,25,26). In addition there was a tumor that was initially considered benign by the histopathologist but later metastasized and so was subsequently considered to have been malignant (18). Including these six tumor cases, the total number of malignant tumors becomes eighteen of 34 and the benign to malign ratio in the literature was 47% to 53%.

It was stated that mitotane was used in two cases with malignant pathology, while two further cases were given chemotherapy, and the final two received radiotherapy. No other treatment methods were mentioned in the other cases. All sixteen of the patients with histologically benign tumors were alive without recurrence of the tumor between one to fourteen years after surgical excision of the tumors. Fourteen out of eighteen patients with malignant tumors were alive

without recurrence of the tumor for varying periods of six months to ten years after removal of the tumors. One of the malignant cases died within sixteen months after disease onset, the other one in the third year, and another died during the resection operation (15,20,27). A case who was considered to be benign on histological examination was followed up with free of metastasis for 7.5 years, but died 8 years after the operation due to disseminated metastasis (18).

Discussion

FATs are exceedingly rare, accounting for 0.37% of 801 adrenalectomies performed between 1970 and 2003 (7). They are usually seen in adult males, and are extremely rarely reported in children. Due to this rarity, FATs are usually reported as single case reports (10,16,19,20,28-40). The larger published series usually include only two or three cases (7,8,15,41,42). There are two exceptions; reviews performed by Gabrilove et al (43) in 1965, which included 52 cases reported before 1965 and another by Chentli et al (44) in 2015 which contains 50 cases reported between 1979 and 2014. These two large reviews mainly involve adult males. To the best of our knowledge, there is no previous study that has summarized pediatric cases of FAT. In this study, we reported two cases of FAT in childhood period and managed at our center, one benign and the other malignant, in two genders with different clinical presentations. We also performed a systematic literature search (Table 2) and reviewed 34 pediatric patients with FAT. Thus, this report focusses on the clinical and hormonal characteristics, as well as treatment options and the follow-up of this rare tumor in the pediatric age group.

FATs were more frequent in boys, accounting for nearly two thirds of all pediatric cases. They are more common in younger children and 85% of cases were under eight years old with most between the ages of 4 and 8. The diagnosis of FATs are based on clinical findings and hormonal evaluation, and estrogen secretion is vital. FATs present with different clinical findings in boys and girls. The two new cases reported in this study highlight the divergence of the presentation of FAT in different genders in children. While boys present with contrasexual pseudopuberty, girls present with isosexual pseudopuberty. All of the boys in the literature, including our first case, had bilateral gynecomastia, which was also painful. Most cases of gynecomastia, including physiological gynecomastia seen during puberty, are caused by an imbalance between estrogen and androgens (45,46). Physiological pubertal gynecomastia is most commonly seen in mid-puberty with Tanner stage 3-4 pubic hair and bilateral testicular volumes

of 5-10 mL. Most adolescents during this period have normal estrogen levels, but a few studies have shown high levels in some cases (47,48,49). Pathological gynecomastia may rarely be seen in adolescents and prepubertal boys. It is related to conditions where there is absolute or relative estrogen excess. Pathological gynecomastia may be seen in cases of exogenous intake of estrogen-containing drugs, the presence of endogenous estrogen-producing tumors, increased peripheral conversion of androgens to estrogens secondary to increased aromatase activity, androgen deficiency or androgen insensitivity (50). Gynecomastia presenting at pre-pubertal ages or with a progressive increase in size at pubertal ages in boys should be raise suspicion of a hormone secreting tumor, especially FAT. In contrast to physiological pubertal gynecomastia in the adolescent period, androgen levels inconsistent with the pubertal stage should be carefully investigated, and tumors need to be excluded. In girls, the main signs associated with FATs were early breast development and/or menstruation. Other signs of precocious puberty, such as increased growth velocity and advanced bone age were observed in both genders. Children rarely presented with the neurological complications of Cushing syndrome, such as delirium and aggressive behavior and signs of high blood pressure (21,51). Although it was very rare in childhood, in advanced stages, some patients also presented with abdominal masses or metastases (16,18,19).

From a hormonal perspective, FATs secrete estrogen alone or in combination with other adrenocortical hormones (mixed secretions). In adults, estrogen secretion is usually isolated but sometimes overt or subclinical hypercortisolism may also be found while other hormone secretions, such as androgen precursors, aldosterone or inhibin, were rarely reported (52,53). Among the previously reported pediatric patients, mixed secretion was often observed and hyperandrogenism due to secretion of adrenal androgen precursors, including 17-hydroxyprogesterone, deoxycorticosterone, 11-deoxycortisol, androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate were more common than overt or subclinical hypercortisolism. While isolated estrogen secretion was reported in a quarter of the cases, 60% had high levels of both estrogen and androgen, and the remaining 15% had cortisol hypersecretion in addition to hyperestrogenism and hyperandrogenism. The two new cases described in this study also had mixed hormone secretion. The male case was found to cosecrete estrogen, cortisol, and androgens whereas in the second case both estrogen and androgen hypersecretion was observed. Contrary to pediatric cases, adult patients with FAT generally have low T levels, attributable to several mechanisms. The first is the hypothalamic inhibition of FSH and LH secretion by estrogen; the second is the inhibition of Leydig cells by high estrogen levels; and the third is an increase in sex hormone binding globulin (SHBG) levels, secondary to excess estrogen (7,52). As SHBG has a high affinity for T, free T levels would fall, leading to findings of hypogonadism (54).

The mechanisms by which FATs cause hyperestrogenism are excessive direct estrogen production by the tumor and enhanced conversion of peripheral androgens to estrogen in adipose tissue (55). Studies have also shown that FATs produces aromatase mRNA, and increased aromatase activity has been reported in patients with FATs and demonstrated *in vitro* (7,56,57). Hypogonadotropic hypogonadism due to inhibition of the hypothalamus-pituitary-gonadal axis and thereby suppressed LH and FSH secretion usually accompany hyperestrogenism (7,56,57). This is important because the gonadotropin level is the only way to differentiate between peripheral, and central precocious puberty as well as normal puberty in children presenting with pubertal findings. In addition, estrogen secretion seen in patients with FATs may remain dependent on pituitary adrenocorticotropic hormone activity and estrogen release from the tumor can be reduced by dexamethasone therapy (54).

The main treatment for FATs, as with other ACTs, is surgical removal of the tumor. It is recommended that at least 90% of the tumor be excised, even in the presence of metastasis (54), as there is a high risk of relapse if not removed. In the literature review, surgical removal of the tumor was attempted in all cases. If complete excision of the tumor is not possible, it is necessary to destroy the remaining tumor tissue and reduce the excess hormones secreted from the tumor. The medical agent frequently used for this purpose is mitotane (ortho paraprime dichloro diphenyl dichloroethane), given its inhibition of hormonal secretion and its cytolytic and adrenolytic properties. Mitotane also induces the formation of free radicals, which in turn inhibit 11-β-hydroxylase and block steroidogenesis (58,59). The male case presented here received mitotane and hydrocortisone 10 mg/m^2/d cover to counter the adrenolytic effect of the mitotane. He was monitored for mineralocorticoid deficiency, although no such findings developed. Mitotane also strongly inhibits 5-α-reductase enzyme activity. In our case this produced an exaggerated elevation of T and its precursors and even estrogen, due to aromatization of excessive androgens. This presented a clinical challenge in the assessment of relapse. Since, the abdominal and thoracal imaging did not reveal any sign of relapse, high levels of T, estradiol and androstenedione were attributed to the inhibition of 5-α-reductase enzyme activity.

This was confirmed by the elevated T/dihydrotestosterone ratio. Subsequently to cessation of mitotane therapy, T and other elevated hormones gradually declined and reached normal values. This phenomenon should be considered in case of unexpectedly elevated androgen with no sign of relapse in conjunction with a history of mitotane treatment. This inhibition may be persistent since mitotane is lipophilic and is therefore metabolized slowly.

Most of the reported cases of FAT in adult patients are malignant, whereas in children benign FATs represented around half of the reported cases. Unfortunately, there are no accepted clinical, radiological or even histological criteria to differentiate benign from malignant tumors, other than its behaviour in terms of recurrence and metastasis. Thus the differentiation between adenoma and carcinoma is usually difficult (8,60). Although the presence of certain histological predictive criteria involving mitotic activity, atypical mitosis, high nuclear grade, low percentage of clear cells, necrosis, diffuse tumor architecture, capsular invasion, sinusoidal invasion, and vascular embolism leans more to the diagnosis of carcinoma, the assessment of malignant potential still depends on clinical behavior of the tumor in children (8). In adult tumors histopathological markers, such as positive immunostaining for aromatase, can help assessment of malignant potential (11). Pediatric cases have been reported in whom a differentiation between benign and malignant could not be made and in one case the tumor was initially considered to be benign, based on histopathological examination, but the tumor turned out to be malignant when metastasis was later detected (18,23,24,25). Therefore, it has been suggested that even in the case of benign histopathological findings, clinicians should have a high degree of suspicion for recurrence/metastasis when there is a tumor secreting estrogen (9). In the first case from our center, the patient already had metastasis at diagnosis and in this case the FAT was malignant which required medical treatment with mitotane as well as chemotherapy. In the second case presented, there was no metastasis or recurrence of the tumor at follow-up, total resection of the primary tumor leading to cure and this tumor had a benign course.

Given the unpredictable nature of these tumors clinical, hormonal, and radiological follow-up after surgical treatment is necessary. As FATs secrete estrogen, postoperative estrogen levels may be used to confirm whether a complete resection of the tumor has been achieved. In the presence of other hormone secretions, the postoperative monitoring of their levels may provide information on any residual tumor. In both presented patients, as well as in the previously reported cases, postoperative hormone levels declined.

However, re-elevation following mitotane therapy, perhaps due to inhibition of 5-α-reductase activity, was observed in the first case. It is recommended to check the hormone profile every three months to screen for recurrence. Imaging with chest and abdomen CT every three months for the first two years, and then every six months for three years, is also recommended in malignant tumors. Annual imaging is recommended after the fifth year (61,62).

In the earlier reports, all but one of the cases classified histologically as a benign tumor were alive without recurrence of the tumor. Although complete surgical resection of benign FATs is thought to be curative, long-term follow-up is required because of the unpredictability of these lesions. Approximately 75-80% of the malignant cases were alive for a period of six months to 10 years after removal of tumor. Five-year survival for these tumors was not calculable since the follow-up periods of all tumors were uncertain. FAT has a better prognosis in children compared to adults, since most diagnoses are made in the early period before puberty. As with other adrenal tumors, FATs in the childhood period tend to occur in pre-pubertal ages, so excess secretion of adrenal hormones is easily noticed before puberty (4,63). Early diagnosis of FAT is important, as tumor size is associated with prognosis. Although there is not much data in the literature on long-term survival rates of pediatric FATs, they are thought to behave like other adrenocortical carcinomas. In general, the survival rate with adrenocortical carcinomas varies according to tumor stage, and the prognosis changes dramatically in the case of metastatic disease. Five-year survival rate was 90% in patients with small, totally resectable tumors, but this fell to 10% in patients with distant metastases (64). Mixed hormone secretion, very high estradiol levels at baseline and large tumor size are all reported to be poor prognostic factors in FATs (7). In the first presented case there were mixed hormone secretion, elevated basal estradiol level, large tumor size, pulmonary metastasis and thrombus in IVC which were all criteria for poor prognosis.

Study Limitations

One of the limitations of the study was that it was conducted retrospectively. The number of patients with FATs were also limited due to rarity of this tumor.

Conclusion

FATs are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia. FATs are more common in children ≤8 years of age, with a median age at diagnosis of six years. While boys present with contrasexual pseudopuberty signs, girls present with

isosexual pseudopuberty. A high estrogen level strongly supports the diagnosis, while elevations in other adrenal hormones may also been seen. FATs are usually malignant in adults whereas in children approximately half of the FATs are benign. The assessment of malignant potential depends on clinical behavior of the tumor in children. Although complete surgical resection of benign FATs is thought to be curative, the long-term follow-up is required because of the unpredictability of these tumors. For treatment of malignant FATs, mitotane or aromatase inhibitors, with or without standard or targeting chemotherapy, in addition to surgical removal, is recommended. The prognosis depends on the stage of the tumor, although it is generally very poor in adult males. FATs occurring in childhood period may carry a better prognosis than in adult males with most pediatric FATs being followed without recurrence since the diagnosis is made early, as typical presenting signs are more obvious before puberty.

Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Ethics Committee (approval number: GO 20/401).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Doğuş Vurallı, Nazlı Gönç, Alev Özön, Saniye Ekinci, H. Serkan Doğan, Serdar Tekgül, Ayfer Alikaşifoğlu, Concept: Doğuş Vurallı, Nazlı Gönç, Ayfer Alikaşifoğlu, Design: Doğuş Vurallı, Nazlı Gönç, Ayfer Alikaşifoğlu, Data Collection or Processing: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Özön, Analysis or Interpretation: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Özön, Literature Search: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Ozon, Writing: Doğuş Vurallı, Ayfer Alikaşifoğlu, Alev Özön, Nazlı Gönç.

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