



Pure androgen secreting adrenal adenoma: a case report and review of literature

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Abstract

Pure androgen secreting Adrenal adenoma is exceptionally rare. Till now only around 20 cases of exclusively androgen secreting adrenal adenomas have been reported in English literature. These tumours may present with virilisation, hirsutism, menstrual abnormalities and even infertility. Various hormonal characteristic including rare presentation of responsiveness to gonadotrophins have been reported. We present here our rare case of virilising purely androgen secreting adrenal adenoma in a 32 year old female and review of literature.

Keywords: HCG, androgen, adrenal, pure, adenoma, rare

Introduction

Virilising tumors in adult females typically arises from ovaries. Adrenal tumor causing virilisation is rare. Among them exclusively androgen secreting tumors are even rarer [1]. Usually adrenocortical carcinoma may present with symptoms of cortisol excess and virilisation. Adrenal adenoma presenting with exclusive androgen production is exceptionally rare. Till now only around 20 cases of exclusively androgen secreting adrenal adenomas have been reported in English literature. These tumors may present with various hormonal characteristics including rare presentation of responsiveness to gonadotrophins being reported. We present here our rare case of a purely androgen secreting adrenal adenoma in a female patient and review of literature.

Case presentation

A 32 year old married female presented with infertility since 2 years and hirsutism, irregular menses, masculine voice since 1 year. She complained of increased hair growth all over her body, mostly on face for which she had to shave daily and she also developed alopecia. She was moderately built and normotensive. On examination, she had male type of pubic hair distribution with clitoromegaly. She did not have any cushingoid features. Laboratory investigations showed serum testosterone level 1.76 ng/ml (0.09-1.09). Dihydroepiandrosterone sulphate (DHEA-S) was found to be raised 1082.2 ug/dl (74-410). Serum cortisol was normal. Serum estradiol was 0.26 nmol/L (0.25-0.40) and serum androstenedione was 7 nmol/L

(1.9-8.9). Low dose dexamethasone suppression test value was 6.40 ug/dl, which was equivocal. Serum follicle stimulating hormone (FSH) and Luteinising hormone (LH) values were normal. Plasma free metanephrine was 29 pg/ml (<90). Plasma Nor-metanephrine was 32.7 pg/ml (<180). Urinary VMA was normal 1.04 mg/day (1.6-7.3). Fasting blood sugar was 71 mg/dl. Ultrasonography showed a well defined, hypoechoic, solid encapsulated left suprarenal mass. Endovaginal scan was normal. Computed tomography (CT scan) Abdomen revealed a 9*8 cms moderately enhancing heterogenous suprarenal mass on left side (Figure 1).

Based on these findings, patient underwent left open Adrenalectomy (Figure 2). Histopathology report came out to be adrenal adenoma (Figure 3). Post-op patient recovered well. On follow up at 4 months her testosterone and DHEA-S values also normalized. Her hirsutism completely disappeared as well as her voice also recovered. She was having regular menstruation and now planning for conception.

Discussion

Virilisation in females can be due to virilisation. Tumors secreting excessive androgen leads to virilisation and other symptoms of androgen excess [1]. Tumors causing virilisation usually originate in ovary. Less commonly, adrenal tumors are responsible for virilisation and usually an adrenocortical carcinoma is the culprit [1]. They are associated with elevated urinary 17-ketosteroid (17-KS) levels and high concentrations

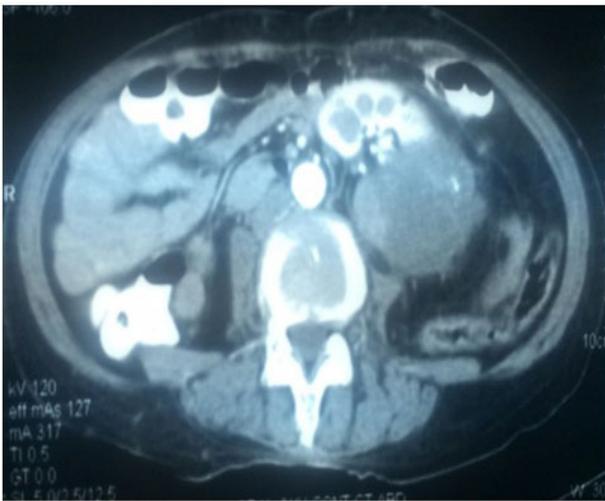


Figure 1. CT scan showing left heterogeneous enhancing adrenal mass.



Figure 2. Cut section of the specimen showing hemorrhagic areas.

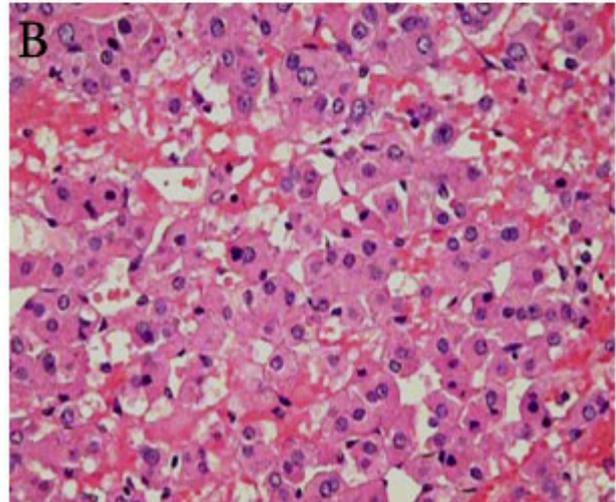
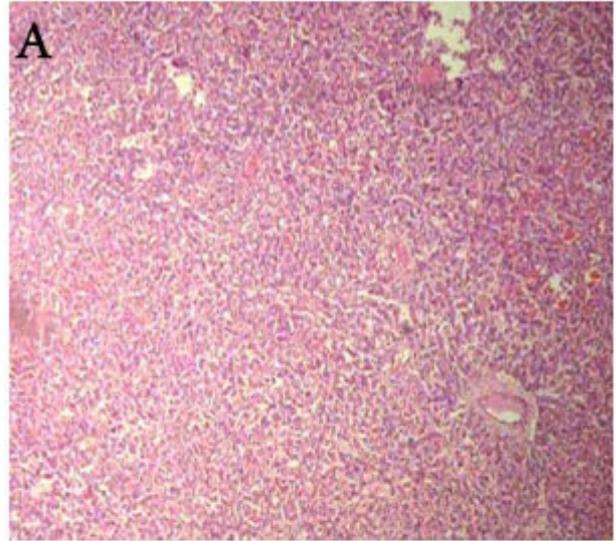


Figure 3. (A) Low magnification H&E stain. Round to oval cells arranged in trabeculae, nesting and alveolar pattern. Large areas of hemorrhage seen. (B) High magnification H&E stain. Round to oval cells with vacuolated lipid rich cytoplasm seen. Few cells showing anisonucleosis. Features consistent with Adrenal adenoma.

of dehydroepiandrosterone (DHEA), androstenedione and testosterone [2]. Normally the adrenal cortex secretes DHEA, androstenedione and estrone (17-ketosteroids, 17-KS). Ovary and testis secrete estradiol and testosterone. Thus, the finding of high levels of testosterone usually points to an ovarian source. However virilisation can also occur with adrenal tumors due to secretion of androstenedione and DHEA (leading to high 17-KS levels), which are peripherally converted to testosterone [1]. Most of the reported testosterone secreting adrenal adenoma are associated with increased urinary 17-KS due to increased secretion of DHEA [3]. Adrenal tumors secreting purely androgens without cortisol and elevated levels of 17-KS are a rarity and pure androgen secreting

adenomas are even rarer. Givens et al., had proposed that the excess serum testosterone with low 17-KS is due to increased enzymatic activity in virilizing adrenal tumours converting the androstenedione (the prevailing adrenal androgen) into testosterone [4]. Kelly et al., also made the observation that there was 50 fold increase in 17-P-hydroxysteroid dehydrogenase activity in the tumor, thus converting androstenedione directly into testosterone [5]. Aguirre and Scully's theorised that the pure testosterone secreting adrenal tumors might have originated from gonadal cells displaced within the adrenal gland [6]. Vasiloff et al., further supported this theory by finding crystalloids specific for gonadal Leydig cells in three cases of virilizing adrenal tumors [7].

Givens et al., were one of the earliest to report a case of purely testosterone secreting adrenal adenoma. The patient had only elevated serum testosterone with normal urinary 17-KS. Dexamethasone suppression test also did not lower the testosterone levels and gonadotrophins increased the testosterone level. The patient underwent bilateral oophorectomy, as an ovarian source was suspected but the testosterone levels were still elevated post-oophorectomy. So the patient underwent adrenal exploration and a 4 cm adrenal tumor was removed which turned out to be an adrenal adenoma [4]. Leinonen et al., also reported on the paradoxical responsiveness of adrenal adenoma to gonadotrophins and demonstrated Human chorionic gonadotrophins (HCG) receptors in the adenoma specimen [8]. Similar gonatrophin responsive tumors were also reported by many authors [2,9-11]. Moreno et al., from Lille, france presented their report of 21 cases of Pure Androgen secreting adrenal tumours (PASATs) in a review of 801 adrenalectomies over a period of 33 years. They found that only 6 patients had adrenal adenoma with the pure androgen secreting profile, which is the largest reported series in English literature. They also concluded that 50% of PASATs are malignant and no biochemical parameter is suggestive of malignancy. All patients had undergone imaging studies and underwent open adrenelectomies [12]. Cordera et al., from mayo clinic recently performed their review of virilising adrenal tumors from january 1946 to November 2002 in which only 2 such cases were reported [1]. The authors concluded that imaging studies are the best method to diagnose the tumour and surgical resection is the standard treatment.

Before the advent of imaging studies like computed tomography scan (CT Scan), Ultrasonography and Magnetic resonance imaging (MRI), we had to rely on dynamic hormonal testing to differentiate adrenal from ovarian source [13].

Dexamethasone suppression test, ACTH/HCG stimulation test were done to find the cause and source of androgen excess [13,14]. However dynamic hormonal testing has been challenged as a means of differentiating between the two sources of hormone production in view of varied tumor responsiveness to hormones and subset of gonadotrophin responsive tumors [4,7,8]. The results of dynamic hormonal testing can be misleading, as too many unnecessary oophorectomies have been performed in literature when the real culprit was the adrenal tumour [4,5,15-17]. Currently the best method to differentiate between adrenal and ovarian source is by modern radiologic techniques such as Ultrasonography, CT Scan, MRI and venous sampling [1]. Modern Imaging techniques can reliably localize the tumor and are currently the investigation of choice for tumor localization and staging. In our case, high serum testosterone level made us to suspect an ovarian source first but the endovaginal scan turned out to be normal and dexamethasone test was equivocal. So we did an abdominal sonography and could find the adrenal tumor on ultrasonography and CT Scan.

Surgical resection remains the primary treatment modality of choice for virilising adrenal tumors. Traditionally open transperitoneal adrenalectomy was the standard procedure of choice but with the advent of laparoscopy, virilising adrenal tumors are being successfully resected laparoscopically much frequently. Prognosis is excellent with surgical Therapy. Postoperatively patients need to be monitored with serial imaging and biochemical tests [1].

To the best of our knowledge, only 20 cases of purely androgen secreting adrenal adenoma have been reported in the English literature so far. If we include case reports with slightly elevated 17-KS another five cases can be included [7]. We have presented all the reported cases with the relevant biochemical profile, treatment and outcome in the **Table 1**.

Table 1. Showing various clinical and biochemical parameters with treatment outcome of reported patients.

Author	Age in years	Sex	Presentation	Serum Testosterone	Serum DHEA-S	17-KS	HCG responsive	Tumor size/side	Treatment	Outcome/ follow up
Givens et al.,	49	F	Virilisation	911 ng/dl	--	N	+	4 cms/R	Oophorectomy + Adrenalectomy	Virilisation reduced/NA
Larson et al., [18]	76	F	Virilisation	9130 pg/ml	-	8.6 mg/24 hrs	-	NA	Adrenalectomy	Alive & Well
Cordera et al.,	27/52	F	NA	Elevated	-	N	NA	6c ms/R 1.5 cms/L	Adrenalectomy	6 months and 118 months, live and well
Dolinar et al., [19]	60	F	Virilisation	650 pg/ml	2100 nmol/l	7.2 mg/24 hours	-	-	Oophorectomy-adrenalectomy	Decreased testosterone
Moreno et al.,	6 patients (17-66)	F	Hirsutism in all, infertility in 2 patients	Elevated	Elevated	N	NA	(4cms -22 cms)	Adrenalectomy	Testosterone normalized in all, 2 died of stroke & CML FU (1-33 years)

Continuation of Table 1.

Author	Age in years	Sex	Presentation	Serum Testosterone	Serum DHEA-S	17-KS	HCG responsive	Tumor size/side	Treatment	Outcome/follow up
Kable et al., [20]	-	F	Virilisation	472 ng/dl	-	14.9mg/24 hrs	NA	-	Adrenalectomy	Alive and well
La 'szlo et al.,	55	F	Virilisation	7.6 ng/ml	220 nmol/l	3.6 nmol/l	+	3 cms/R	Flutamide Adrenelactomy	Hirsutism decreased at 4 months
Spaulding et al., [21]	-	F	Virilisation	500 ng/dl	N	7.3		1 cm/R	Laparoscopy and adrenalectomy	NA
Rodríguez Gutiérrez et al., [22]	18	F	Virilisation and hypertension	4.3 ng/ml	1000 u/dl	25 ng/dl	NA	10 cms/L	Adrenalectomy	Alive and off anti hypertensive drugs at 2 months
Kelly et al.,	-	F	Virilisation	285 ng/dl	N	N	-	-	Adrenalectomy	Alive and well
Leinonen et al.,	60	F	Virilisation	17.8 nmol/l	630 nmol/l	NA	+	NA/R	Hysterectomy, B/L oophorectomy, adrenelectomy	NA
Themis et al., [23]	15	F	Virilisation	elevated	N	N	-	-	Adrenalectomy	Attained puberty and menses at 4 months
Vasiloff et al.,	49	F	Virilisation	1408 ng/dl	NA	11.1 mg/24 hrs	-	4 cms/R	adrenalectomy	NA
Smith et al.,	50	F	virilisation	970 ng/dl	2300 nmol/l	11.2 mg/24 hours	+	NA	Adrenelecto,y	NA
Current case	32	F	Viruilisation, infertility	1.76 ng/ml	1082 ug/dl	N	-	9 cms/L	Adrenlectomy	Decease in hirsutism, normal testosterone at 4 months

Conclusion

Pure androgen secreting adrenal adenoma is a very rare presentation. Dynamic endocrine testing cannot be relied upon for its diagnosis. Radiological imaging studies are currently the standard tests for localizationnd diagnosis along with endocrinologic studies. Surgical resection remains the standard treatment.

List of abbreviations

DHEA-S: Dihyrdoepiandrosterone sulphate
 FSH: Follicule stimulating hormone
 LH: Luteinising hormone
 CT scan: Computedtomography
 17-KS: 17-ketosteroid
 HCG: Human chorionic gonadotrophins
 PASATs: Pure androgen secreting adrenal tumours
 MRI: Magnetic resonance imaging

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	GG	SY	SV	NA	SSY	VT
Research concept and design	✓	--	--	--	--	--
Collection and/or assembly of data	--	✓	✓	--	--	--
Data analysis and interpretation	--	--	--	--	--	--
Writing the article	✓	✓	--	--	--	--
Critical revision of the article	--	--	--	✓	✓	--
Final approval of article	✓	--	--	--	--	✓

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