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A patient with refractory testicular adrenal rest tumour in the setting of cyp11b1 deficiency congenital adrenal hyperplasia

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Abstract

Testicular adrenal rest tumour (TART) due to CYP11B1 deficiency is a very rare clinical finding. Only seven cases have been reported previously. Here, the case of a 19-year-old boy with classic CYP11B1 deficiency and large testicles refractory to medical treatment that led to orchidectomy is reported. The clinical and laboratory manifestations of this patient are discussed and compared with that of the previously reported cases. The patient presented with rapid body growth, precocious puberty, hypertension, recurrent hypokalaemic paralysis and testicular enlargement. The most important differential diagnosis of his latter presentation is Leydig cell tumour (LCT). It was found that positive family history of congenital adrenal hyperplasia (CAH), hypertension, bilaterality, hypokalaemia and multiple hypoechoic masses on ultrasonography of the testes are in favour of a diagnosis of TART. Conversely, high titres of tumour markers and presence of Reinke crystalloids are supportive of a diagnosis of LCT.

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Rare disease

A patient with refractory testicular adrenal rest tumour in the setting of cyp11b1 deficiency congenital adrenal hyperplasia

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bstract

Testicular adrenal rest tumour (TART) due to CYP11B1 deficiency is a very rare clinical finding. Only seven cases have been reported previously. Here, the case of a 19-year-old boy with classic CYP11B1 deficiency and large testicles refractory to medical treatment that led to orchidectomy is reported. The clinical and laboratory manifestations of this patient are discussed and compared with that of the previously reported cases. The patient presented with rapid body growth, precocious puberty, hypertension, recurrent hypokalaemic paralysis and testicular enlargement. The most important differential diagnosis of his latter presentation is Leydig cell tumour (LCT). It was found that positive family history of congenital adrenal hyperplasia (CAH), hypertension, bilaterality, hypokalaemia and multiple hypoechoic masses on ultrasonography of the testes are in favour of a diagnosis of TART. Conversely, high titres of tumour markers and presence of Reinke crystalloids are supportive of a diagnosis of LCT.

BACKGROUND

Testicular adrenal rest tumour (TART) is a rare entity, particularly in CYP11B1 deficiency.[1] We found only seven cases of TART due to CYP11B1 deficiency previously reported in the literature.[2–7] The appropriate treatment of TART is suppression of adrenocorticotropic hormone (ACTH) by administration of glucocorticoids. Sometimes, concerns about malignancy may lead to surgical intervention because the most important differential diagnosis is Leydig cell tumour (LCT).[1,8,9] Unnecessary orchidectomy, as in our case, may be prevented by comparing clinical and paraclinical findings of TART and LCT.

Here, we present clinical and laboratory manifestations of a patient with TART and compare them with those of the previously reported cases. Then, we discuss features helping to differentiate TART from LCT, and factors predicting poor medical response.

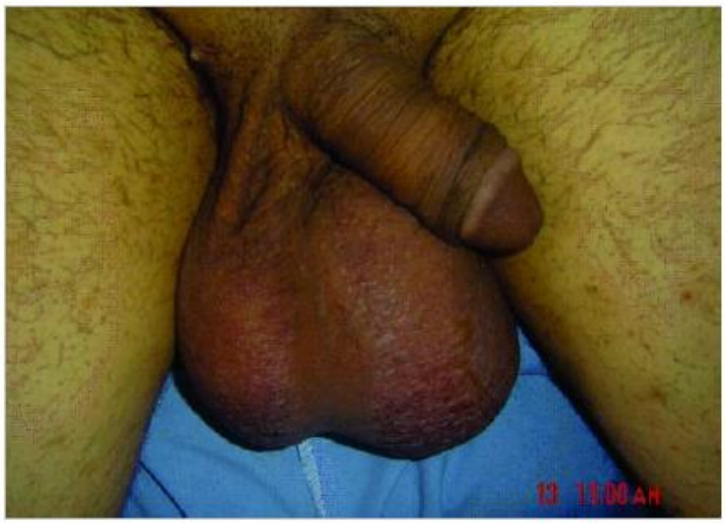
CASE PRESENTATION

A 19-year-old boy, a candidate for orchidectomy because of his large testes, was referred to us, at the department of endocrinology and metabolism of St Alzahra University Hospital, Isfahan, Iran, for preoperative evaluation of hypokalaemia and hypertension. During infancy, he presented with developmental delay in neck support, walking, speech and urinary continence. At 4 years old, his parents noted increased pubic hair, enlargement of the testes and phallus, rapid body growth and polyphagia. These complaints led to hospitalisation at 5 years of age. Physical examination at this time detected adult type genitalia, masculinisation and skin pigmentation. Blood pressure was 140/115 mm Hg. Weight, height and bone age were 39 kg (>95th percentile), 135 cm (>95th percentile) and 156 months, respectively. Serum potassium was 3.4 mEq/litre (3.5–5). Ultrasonography showed bilateral adrenal enlargement and normal kidneys. The diagnosis of classic CYP11B1-deficient congenital adrenal hyperplasia (CAH) was considered and dexamethasone was added to antihypertensive medications. His parents wilfully discontinued the medication shortly thereafter. Despite the slow growth rate of their son, they did not seek medical care until the age of 13, when he was affected by recurrent paralytic attacks due to severe hypokalaemia. Serum potassium was reported as low as 1.5 mEq/litre and blood pressure was recorded as 170/130 mm Hg. The diagnosis was hypokalaemic paralysis due to CAH. After correction of hypokalaemia and hypertension, he was discharged from the hospital. The patient and his parents were advised to better comply with the prescribed medications and follow-up. Unfortunately, they did not adhere to this advice and again discontinued medications. Despite that, neither the patient nor his parents reported any significant new problems until age 15. At 15, both testes gradually began to enlarge, and this led to hospitalisation at 19. When we visited the patient in the endocrine ward, he had short stature (146 cm), was deeply hyperpigmented and fully virilised. This complete virilisation despite low serum testosterone, as we present later, was considered a clinical manifestation of high adrenal androgens. His blood pressure was 160/90 mm Hg. Acne was observed on his face, neck and upper thorax. Thyroid size was normal. His phallus in stretched position was 16 cm. The right and left testes sized 2×3×4 cm and 4×5×6 cm, respectively (fig 1). Both testes were firm with irregular margins.

Figure 1

Testicular enlargement in a 19-year-old boy with CYP11B

Figure 1



Testicular enlargement in a 19-year-old boy with CYP11B1 deficiency.

1 deficiency.

The patient had 12 siblings, 7 of whom died before 15 months old. One of the seven, who died at 15 months old following vomiting and diarrhoea, had ambiguous genitalia. The patient has four more sisters and one more brother, who are all living and healthy. His oldest brother is 23 years old, with normal stature. The patient's father is the only living kin in his family other than siblings. All of his siblings had also died in the first year of their lives. The patient's parents are genetically relatives.

We prescribed prednisolone (7.5 mg/day), spironolactone (25 mg/twice a day) and amlodipine (5 mg/twice daily), and recommended his urologist to biopsy the testes and postpone orchidectomy. The patient did not agree to a testicular biopsy.

Thereafter, he was under the supervision of his doctor to control the hypertension. We do not know of his compliance over the following 6 months, prior to the next instance of hospitalisation.

INVESTIGATIONS

In laboratory evaluation, α-fetoprotein (aFP), human chorionic gonadotropin (βHCG), serum parathyroid hormone (PTH) and HCO_3 were in the normal range, but follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone, ACTH, basal cortisol and 17OH-progesterone were 84 mIU/ml (normal 1.3–11.8), 100 mIU/ml (2.8–6.8), 2 ng/ml (1.5–6), 495 pg/ml (4.8–49), 5.0 µg/dl (5–25) and 23.8 ng/ml (0.5–2.1), respectively. Potassium was 2.8 mEq/L. Ultrasonography showed heterogeneous multiple hypoechoic masses in both testes, with

numerous calcifications up to 1.4 cm in largest diameter. An abdominal CT scan showed normal kidneys and bilateral adrenal enlargement.

The patient came back to our department 6 months later without significant decrease in testicular size. New laboratory findings, including ACTH, αFP, βHCG and LDH were in the normal range, but FSH and LH concentrations were still elevated. Repeated ultrasonography of the testes detected no changes compare to the previous evaluation. Homogenous pituitary enlargement was visible on MRI.

DIFFERENTIAL DIAGNOSIS

At this stage, the most important differential diagnosis was Leydig (interstitial) cell tumour.

TREATMENT

As we did not observe any significant decrease in testicular size, we were worried about the presence of malignancy; therefore, we decided to perform an orchidectomy. A left radical orchidectomy was done. Gross pathological evaluation showed 7×6×4 cm testis. Normal testicular architecture was replaced by yellow/brown masses with fine septae. Microscopic sections revealed nests, sheets and cords of polygonal cells with abundant granular eosinophilic cytoplasm and round to oval nuclei. No mitotic figures were seen and no Reinke crystalloids, Lipochrome pigment or calcification were noted. Sections from the adjacent testicular tissues showed tubules lined by atrophic epithelium and absence of normal spermatogenesis.

After surgery, dexamethasone (1 mg) was added to antihypertensive drugs.

OUTCOME AND FOLLOW-UP

The patient is now under good blood pressure control and his serum potassium concentration is normal at frequent measurements. The skin pigmentation and acne have improved. We have not observed significant enlargement in the size of the right testis.

DISCUSSION

The present report reveals a refractory adrenal rest tumour in a patient with CYP11B1-deficient CAH. As stated, CYP11B1-deficient CAH is a rare autosomal recessive disease, which accounts for 8% to 16% of CAH cases.[1] This rare disease is relatively prevalent among the Turkish population and Iranian and Moroccan Jews.[1,3,10] In this disease, conversion of 11-deoxycortisol to cortisol and conversion of 11-deoxycorticosterone to corticosterone and aldosterone decreases due to a defect in 11β-bydroxylase activity. Low serum cortisol concentration is a potent stimulator of ACTH secretion that results in adrenal tissue hyperplasia.[3] Adrenal tissues nest mainly in the adrenal gland and ectopically in the hillum of the testis,[11] spermatic cord,[12] and

retroperitoneal space.[13] These tissues probably derive from pleuripotential cells of the urogenital ridge,[4] the common origin of adrenal cortex and testis. These ectopic adrenal cells finally regress with advancing age in all but CAH,[4,14] where they may persist owing to continuous trophic effects of high serum ACTH. Adrenal tissue hyperplasia results in overproduction of intermediate bioactive substances (eg, 11-deoxycortisol, 11-deoxycorticosterone and 17-OH pregnenolone), which lead to hypertension, hypokalaemia and precocious puberty.[3]

Enlargement of the testes due to hyperplasia of ectopic adrenal cells is a rare complication of CYP11B1-deficient CAH. The prevalence of TART due to CYP11B1-deficient CAH is unknown, but in CYP21A2-deficient CAH it has been reported to be as high as 29% by ultrasonography and only 5% by palpation.[15] To the best of our knowledge, this is only the second Iranian and eighth worldwide report on a patient with TART due to CYP11B1 deficiency CAH (table 1).

Table 1: Clinical and imaging data of patients with testicular rest tumour due to CYP11B1-deficient CAH

Cases/reference	Age of TART presentation	Age of CAH diagnosis	Testes size	Palpation	US	Bilateral testicular mass	Family history of CAH	Compliance to treatment	Response to treatment
Bricaire and Luton[2]	17	4	Enlarged	Irregular, hard	NP	+	+	Poor	Marked
Willi *et al*[7]	12	2	9 ml	Normal	ALT	+	+	Poor	ND
Willi *et al*[7]	19	5	11 ml	Irregular, hard	ALT	+	+	Poor	Partial
Srikanth *et al*[6]	>13	3	ND	Irregular, hard	NP	–	ND	Poor	Delayed
Oberman *et al*[5]	13	13	R=10×4×4 cm, L=12×7×6 cm	Irregular, hard	NP	+	+	Poor	Marked
Karnak *et al*[4]	17	2	7.5×4×4 cm	Irregular, hard	ALT	+	+	Poor	Marked
Ghazi *et al*[3] (Iran)	15	2	>25 ml	Irregular, hard	ALT	+	–	Poor	Marked
Present case	15	4	L=7×6×4 cm	Irregular, hard	ALT	+	+	Poor	None

ALT, adrenal-like tissue; CAH, congenital adrenal hyperplasia; ND, no data; NP, not performed; TART, testicular adrenal rest tumour; US, ultrasound.

Clinical and imaging data of patients with testicular rest tumour due to CYP11B1-deficient CAH

In these eight cases, CYP11B1-deficient CAH was diagnosed at ages 2–5 and testicular mass in the second decade.[2–7] Testicular enlargement is almost always bilateral and usually slow growing, although, the rapid growing masses in a non-compliant period of CAH were described by Avila *et al*.[15] The possibility of malignant transformation cannot be excluded in CAH with testicular enlargement, as two cases have been reported in the literature (data not shown).

Ultrasonography is a useful mean for early detection of the TART.[3] In male patients with CAH, it is reasonable to examine the testes clinically and ultrasonographically at the first visit of the second decade and, as Avila *et al* suggested, every 6 months thereafter.[15] Detection of any mass mandates more evaluation to differentiate TART from other causes of testicular enlargement, such as malignancies.

As mentioned, the most important differential diagnosis is Leydig (interstitial) cell tumour. The clinical findings in favour of TART are positive family history, blood pressure changes (eg, elevation in CYP11B1 deficiency) and bilaterality. Positive family history of CAH was reported in almost all cases. By contrast, recurrence and metastasis are characteristics of testicular malignancies. Although the bilateral involvement of testes is in support of TART, but, LCT also may presents as bilateral masses in 3% of cases.[4] Conversely, TART due to CYP11B1 deficiency is reported as a unilateral mass in one of the eight reported cases.[6] TART and LCT usually present as testicular mass in early adulthood. Precocious puberty and gynaecomastia may occur in the course of both.[4,9] The laboratory findings supporting TART are hypokalaemia and normal tumour markers (eg, βHCG, αFP and LDH). Ultrasonographically, TART most often presents as multiple hypoechoic masses versus single hypoechoic mass in LCT.[15,16] Multiple hypoechoic masses and calcified nodules were found in the ultrasonographic evaluation of our patient. Srikanth *et al* reported calcified nodules in gross pathological examination of enlarged testes due to TART,[6] but, it is the first report of this finding in ultrasonographic evaluation of these patients. Histopathologically, TART usually presents as multiple brown/green nodules. Conversely, LCT usually shows as a single brown mass in gross pathology. The brown/green colour is the usual reported colour of TART,[12] which is different from brown colour of LCT[9] and yellow/brown colour of our patient. A yellow/brown colour of TART nodules has already been reported by Srikanth *et al*,[6] but Karnak *et al* also reported such a colour in a Leydig cell tumour.[4] Microscopically, TART has eosinophilic stained cytoplasm, sometimes with lipochrome pigments, but LCT reveals acidophilic or clear cytoplasm with Reinke crystalloids and sometimes lipochrome pigments, similar to TART. Reinke crystalloids are not a usual finding of TART, but a specific microscopic finding of Leydig cell tumour, which is sometimes present.[9] Neither Reinke crystalloids nor lipochrome pigment were seen in our patient.

Extensive fibrosis and calcification of testicular adrenal rest tumour predict poor, if any, response to medical treatment.[6] In our patient, replacement of original testicular tissue by adrenal rest tumour resulted in testicular failure. This was confirmed by high serum levels of FSH and LH in the presence of low serum testosterone concentration and atrophic semeniferous tubules with no spermatogenesis in microscopic examination. Karnak *et al* reported good medical

response in a patient with CAH who had mildly increased FSH and LH,[4] but moderate to high serum gonadotropin concentration may predict poor response to medical treatment in TART.

In contrast to our case, almost all previously reported cases showed marked to partial response to prolonged ACTH suppressive therapy. At the presentation of testicular enlargement, our patient had some aspects of poor response to medical treatment. These were poor compliance, testicular failure, firmness of testes, extensive fibrosis and calcification. We suggest these as probable poor response criteria, although a 6 month course of treatment is relatively too short to come to this conclusion. In the presence of these findings, we strongly recommend more prolonged ACTH suppressive therapy and intensified doses of corticosteroids after excluding malignancy by biopsy and before deciding on further surgical intervention.

In conclusion, although differentiation between TART and LCT is difficult, some findings such as family history, hypertension, bilaterality, metastasis, tumour markers, serum potassium, sonographic images and Reinke crystalloids in pathology can favour the diagnosis toward one or the other.

LEARNING POINTS

- CYP11B1 deficiency presents in men with pseudo precocious puberty, hypertension and hypokalemia, due to increased androgen and mineralocorticoid steroid precursors.
- Non-compliance with glucocorticoid suppressive therapy may increase the likelihood of developing adrenal rest tumours within the testes.
- The main differential diagnosis for adrenal rest tumour is a Leydig cell tumour.
- Extensive testicular infiltration with adrenal rest tumours may lead to primary testicular failure, testosterone deficiency and infertility.

Footnotes

Competing interests: none.

Patient consent: Patient/guardian consent was obtained for publication.

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