BILATERAL ADRENAL AND TESTICULAR MASS IN A PATIENT WITH CONGENITAL ADRENAL HYPERPLASIA

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Abstract

Introduction. Congenital adrenal hyperplasia (CAH) autosomal recessive disorders characterized by impaired adrenal steroid hormone synthesis. The most common form is 21-hydroxylase deficiency (21OHD). Testicular adrenal rest tumors (TARTs) are benign intratesticular masses that occur in male patients with CAH. TARTs are quite common in patients with 21OHD who were diagnosed late.

Case report. A 41-year-old male patient with CAH secondary to 21OHD. The patient was referred to our endocrinology department from the andrology clinic for bilateral adrenal masses. Bilateral orchiectomy had been performed due to bilateral testicular masses and azoospermia two years ago. The pathology was reported as Leydig cell tumor. In hormonal assessment, baseline cortisol levels were low, 17-hydroxyprogesterone levels with baseline and after cosyntropin stimulation test were high. As a result of clinic and laboratory assessment, the patient was diagnosed with simple virilising CAH due to 21OHD and adrenal insufficiency. Then, prednisolone replacement was initiated. Bilateral orchiectomy tissue blocks of the patient were re-assessed and were considered TART. Magnetic resonance imaging revealed bilateral adrenal masses with 88x55 mm on the right and 41x22 mm on the left. Laparoscopic right adrenalectomy was applied and pathology was reported as myelolipoma. Follow-up of the mass on the left adrenal gland is ongoing. The patient is monitored under prednisolone and testosterone replacement therapy. Early diagnosis of CAH is very important because of the complications it causes. It should be considered especially for bilateral testicular and/or adrenal masses. Both fertility and adrenal glands can be protected with an early diagnosis and an early glucocorticoid replacement.

Key words: Congenital adrenal hyperplasia, Testicular adrenal rest tumors, Myelolipoma, Bilateral adrenal masses.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disorder affecting adrenal steroid synthesis (1). The most common form is 21-hydroxylase deficiency (21OHD) and responsible for 95% of cases (2). In affected patients, glucocorticoid insufficiency due to enzyme deficiency causes ACTH increase. Increased ACTH causes also an increase in adrenal androgen and results in adrenal hyperplasia (3, 4).

Testicular adrenal rest tumors (TARTs) are benign intratesticular masses that occur in male patients with CAH. Elevation of plasma ACTH levels causes hyperplasia not only in the adrenal gland, but also in other tissues sensitive to ACTH like testis. TARTs are ACTH-dependent in that may develop during periods of sustained elevation of plasma ACTH levels. TART frequency reaches up to 90% in male patients with CAH (5-8). These are benign tumors that form as a result of insufficient glucocorticoid replacement; however, it is difficult to distinguish them from Leydig cell tumor (LCT) which is the most common stromal testicular tumour (9, 10). TARTs may cause infertility by inducing testicular atrophy because of the mass effect (11). Therefore, it is important to recognize TARTs.

Early diagnosis of CAH and early initiation of treatment in male patients are very important because of serious complications. We report a male patient with CAH who developed complications in the consequence of late diagnosis.

CASE REPORT

A 41-year-old male patient was sent to our endocrinology department from the andrology clinic for incidentally detected bilateral adrenal masses.

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The patient had history of precocious puberty with short stature as per his peers. There was no history of adrenal crisis requiring hospitalization. Azoospermia and bilateral testicular masses were identified in the patient who was admitted to the andrology clinic with the complaints of infertility. In scrotal ultrasonography (USG), hypoechoic heterogeneous lesions were defined in the right and left testes as approximately 5x4 cm and 3x3 cm, respectively. Then, right orchiectomy was applied to the patient two years ago and then left orchiectomy was also performed to the patient whose diagnosis of the right testicular pathology was LCT. The patient was consulted in the endocrinology department for bilateral adrenal masses which were incidentally detected during follow-up for LCT in abdomen USG.

In the physical examination at endocrinology department, body height was 149 cm and weight was

88 kg. He had generalized hyperpigmentation that was more marked on gingival mucosa and frictional sites. His blood pressure was normal. In other systems' examination was normal. Serum electrolytes were normal in laboratory examination. Baseline cortisol was low, ACTH and 17-hydroxyprogesterone were high. Other hormonal assessment was normal. The patients' baseline laboratory tests are given in Table 1. Stimulation test with 250 mcg cosyntropin was performed, and blood samples for 17-hydroxyprogesterone and cortisol were obtained at 0, 30, and 60 minutes. After stimulation test, 17-hydroxyprogesterone and cortisol levels were 18.2 ng/mL and 4.41 µg/dL at 60th minute, respectively. As a result of clinic and laboratory assessment, the

Figure 1. Magnetic resonance imaging features of bilateral adrenal masses (white arrow); 88x55 mm on the right adrenal mass and 41x22 mm on the left adrenal mass with hypointense signal on T1-weighted sequence (A) and hyperintense signal on T2-weighted sequence (B).

Figure 2. Histological hematoxylin-eosin stained features of testicular adrenal rest tumor cells around the rete testis (A), large magnified view of eosinophilic polygonal cells without Reinke crystals (B), immunohistochemical evaluation diffuse positive reactivity to CD56 (C), diffuse positive inhibin alpha (D), diffuse vimentin (E).

Table 1. The results of baseline laboratory tests

	Result	Reference Range
Glucose	101	74-106 mg/dL
Creatinine	1.1	0.7-1.2 mg/dL
ALT	28	10-36 U/L
Sodium	142	136-145 mmol/L
Potassium	5.08	3.5-5.1 mmol/L
Hemoglobin	14	12.9-15.9 g/dL
Hematocrit	40	39-49 %
Free T4	1.31	0.93-1.7 ng/dl
TSH	1.69	0.27-4.2 µu/mL
FSH	33.5	1.2-19.2 mIU/mL
LH	17.2	1.24-8.62 mIU/mL
Progesterone	46.3	0.05-0.14 ng/mL
Total testosterone	1.79	2.18-9.06 ng/mL
DHEA-S	310	88.9-427 µg/dL
Cortisol	3.75	6.2-19.4 µg/dL
ACTH	80.4	9-46 pg/mL
IGF-1	243	94-210 ng/ml
17 OH Progesterone	14	0.2-2.3 ng/mL
Aldosterone	10	3.7-43.2 ng/dL (Upright)

ACTH; Adrenocorticotrophic hormone, ALT; Alanine aminotransferase, DHEA-S; Dehydroepiandrosterone sulphate, FSH; Follicle-stimulating hormone, IGF-1; Insulin-like growth factor, LH; Luteinizing hormone, TSH; Thyroid-stimulating hormone,

patient was diagnosed with simple virilising CAH due to 21OHD and adrenal insufficiency. Because, 17-hydroxyprogesterone levels after cosyntropin stimulation test >15 ng/mL confirm the CAH diagnosis (1).

Prednisolone 5 mg/day was initiated and bilateral orchiectomy materials of the patient were re-assessed. Macroscopically both testis specimens (right testis: 2,8 cm and left testis: 1,6 cm) appeared brown firm and cut surface lobulated. In microscopic examination, normal testicular tissue was replaced by LCT like tumour morphologically. The LCT like tumour cells resemble sheets and nests of large polygonal and round cells with defined cell borders, abundant eosinophilic cytoplasm and round central nuclei (Fig. 2A). In addition, the lack of reinke crystals also supported the TART diagnosis (Fig. 2B). Immunohistochemical analyses were performed and the polygonal cells showed positivity for CD56 (Fig. 2C), inhibin alpha (Fig. 2D), vimentin (Fig. 2E). These all findings support the TART diagnosis (12).

Abdomen magnetic resonance imaging (MRI) scan showed bilateral adrenal masses with hypointense signal on T1-weighted sequences and hyperintense signal on T2-weighted sequences. The sizes of the masses were 88x55 mm on the right adrenal and 41x22 mm on the left adrenal (Fig. 1). Urinary excretion of metabolites of catecholamines was normal. It was thought that bilateral adrenal masses were related to CAH. It was decided to operate the mass of 88 mm diameter since it was large, with nonadenomatous imaging characteristics and had a possible malignancy risk. Laparoscopic right adrenalectomy was applied with glucocorticoid support. His pathology was reported as myelolipoma. Macroscopical examination of right adrenal gland was 8x7x5 cm diameter and microscopical examination showed islands of hematopoietic cells and mature fat.

The patient is monitored under prednisolone and testosterone replacement therapy. Follow-up of the mass on the left adrenal gland is ongoing.

DISCUSSION

Our patient was a late-diagnosed male CAH in which chronic complications developed. The most common form of CAH is 21OHD caused by loss-of-function mutations in CYP21A2 gene (1, 13). There are two main forms of 21OHD as salt-wasting and simple virilising. The type of our patient is the simple virilising form that is commonly seen among adults (1). This form can be early diagnosed in females since

it has serious effects on female sexual development; however, in males it is frequently late-diagnosed because hyperandrogenism could be overlooked (7). In our case, permanent infertility developed due to the late-diagnosis.

In male patients with simple virilising CAH, adrenal crisis is quite rare contrary to the salt-wasting form and the most important complication of this form is gonadal dysfunction and infertility based on TARTs (14). These tumors were first reported in 1940 by Wilkins *et al.* (15). It is thought that adrenal rest tissues in testicular parenchyma are stimulated by their own ACTH receptors and produce steroid hormones. The rising of ACTH synthesis results in hyperplasia of ACTH sensitive tissues in testes and other sites (16, 17). These tumors are benign but they can cause an obstruction and both normal and surrounding testicular tissues due to mass effect. Longstanding obstruction of the seminiferous tubules finally lead to oligoasthenozoospermia, tubular hyalinization and peritubular fibrosis (12, 14). Besides mass effect, TART may also have a paracrine effect on the surrounding testicular tissue. Paracrine secretion of steroid hormones produced by the tumor cells and excessive glucocorticoid replacement may be toxic to the Leydig cells and/or germ cells (18). Our patient is also admitted to the hospital for infertility.

Another reason why these tumors are important is that they are confused with LCT (10). Although it is hard to distinguish them exactly, TARTs are often bilateral and LCTs are often unilateral. Reinke crystals, which can be found in 25-40% of LCT, are absent in TART. In TART cases immunohistochemically, CD56 was diffusely and strongly positive in TART, but only focally and weakly to moderately positive in LCT. The polygonal cells showed positivity to four markers known to be shared between LCT and TART namely inhibin alpha, melan A, vimentin, and calretinin. Inhibin-alpha, an often utilized positive stain in Leydig cell tumors, will also be positive in testicular tumor of the adrenogenital syndrome (12). The biggest difference between them is that while almost 10% of LCT may involve malignant degeneration, TART is almost always benign (14). When unilateral orchiectomy pathology was interpreted as LCT in our case, orchiectomy was applied also to the other side due to risk of malignancy. However, after our patient was diagnosed CAH, orchiectomy materials were re-assessed by the pathology clinic and they thought that it was most likely TART.

In the literature, the authors suggested that the TART should be divided into five stages (14).

According to this, adrenal rests are not detectable in stage 1, stage 2 is the hyperplasia and hypertrophy of adrenal rests, there is a compression of the rete testis in stage 3, peritubular fibrosis and focal lymphocytic infiltrates is observed by progressive obstruction of testicular tissue in stage 4 and stage 5 is characterized by irreversible damage of testicular parenchyma. Early glucocorticoid treatment should be initiated to prevent the progression of testicular damage (17). However, in the fourth and fifth stages of TART, it is not observed the shrinkage of testicular tumours as response to the treatment with increasing dose of glucocorticoid (14). When our case was diagnosed, he was probably in an irreversible period in which it does not respond to treatment. In the advanced stages, testis protective surgery is recommended in order to decrease the mass effect. Some specialists recommend surgery also in early stages because of the side effects of the long term or high dose glucocorticoid treatment (6, 19). It has been shown that high dose glucocorticoid has negative effects on peak bone mass and metabolic parameters especially in children and adolescents (20). In our patient, since the testicular masses were prominent and he was operated without being diagnosed CAH, unfortunately instead of testis protective surgery, bilateral orchiectomy has been applied to him.

One of the CAH complications is bilateral adrenal hyperplasia caused by longstanding ACTH hypersecretion (3, 4, 21). Tumoral formation may develop in a hyperplastic adrenal cortex (4). The high prevalence as 45-82% of these adrenal tumours detected by CT or MRI has been reported in patients with CAH (22, 23). In advanced CAH cases, the probability of malignancy in bilateral adrenal masses is very low and they are often reported as a myelolipoma (4). One study indicated that myelolipoma was detected in 6% of patients with CAH (23). In our case we decided right adrenalectomy both because of the right adrenal tumor diameter and nonadenomatous aspect. Pathological examination was reported as myelolipoma. Adrenal myelolipomas are benign tumors consisted of mature adipose cells and hematopoietic tissues (24). In CAH cases; adrenal myelolipomas are frequently seen bilaterally. Their pathogenesis is not known exactly but it is thought that they are formed from embryonic bone marrow rests or adrenocortical metaplasia (25). In treatment-resistant cases and in tumors progressing despite glucocorticoid treatment, if there are noticeable intratumoral heterogeneity, haemorrhage or other suspicious features, adrenalectomy in CAH is recommended (1). For these reasons, the patient

underwent right adrenalectomy. The pathology of the right mass resulted as myelolipoma, so we decided to follow-up the left adrenal mass under glucocorticoid replacement.

In conclusion, although male CAH cases are rare, early diagnosis of CAH is very important because of the complications it causes. This diagnosis should be considered especially for bilateral testes and/or adrenal masses. Both fertility and adrenal glands can be protected with an early diagnosis and an early glucocorticoid treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018; 103(11):4043-4088.
2. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev*. 2000; 21:245-291.
3. Wang J, Bissada MA, Williamson HO, Yakout H, Bissada NK. Adrenal tumors associated with inadequately treated congenital adrenal hyperplasia. *Can J Urology* 2002; 9: 1563-1564.
4. Barzon L, Maffei P, Sonino N, Pilon C, Baldazzi L, Balsamo A, Del Maschio O, Masi G, Trevisan M, Pacenti M, Fallo F. The role of 21-hydroxylase in the pathogenesis of adrenal masses: review of the literature and focus on our own experience. *J Endocrinol Invest*. 2007; 30:615-623.
5. Stikkelbroeck NM, Otten BJ, Pasic A, Jager GJ, Sweep CG, Noordam K, Hermus ARJ. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2000; 86:5721-5728.
6. Claahsen-van der Grinten HL, Sweep FC, Blickman JG, Hermus AR, Otten BJ. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Eur J Endocrinol*. 2007; 157:339-344.
7. Bouvattier C, Esterle L, Renoult-Pierre P, de la Perrière AB, Illouz F, Kerlan V, Pascal-Vigneron V, Drui D, Christin-Maitre S, Galland F, Brue T, Reznik Y, Schillo F, Pinsard D, Piguel X, Chabrier G, Decoudier B, Emy P, Tauveron I, Raffin-Sanson ML, Bertherat J, Kuhn JM, Caron P, Cartigny M, Chabre O, Dewailly D, Morel Y, Touraine P, Tardy-Guidollet V, Young J. Clinical Outcome, Hormonal Status, Gonadotrope Axis, and Testicular Function in 219 Adult Men Born With Classic 21-Hydroxylase Deficiency. A French National Survey. *J Clin Endocrinol Metab*. 2015; 100(6):2303-2313.
8. Falhammar H, Nyström HF, Ekström U, Granberg S, Wedell A, Thorén M. Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia. *Eur J Endocrinol*. 2012; 166:441-449.
9. Stikkelbroeck NM, Hermus AR, Suliman HM, Jager GJ, Otten BJ. Asymptomatic testicular adrenal rest tumours in adolescent and adult males with congenital adrenal hyperplasia: basal and follow-up investigation after 2.6 years. *J Pediatr Endocrinol Metab* 2004; 17:645-653.

10. Martinez-Aguayo A, Rocha A, Rojas N, García C, Parra R, Lagos M, Valdivia L, Poggi H, Cattani A. Testicular adrenal rest tumors and Leydig and Sertoli cell function in boys with classical congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2007; 92:4583–4589.
11. Reisch N, Flade L, Scherr M, Rottenkolber M, Pedrosa Gil F, Bidlingmaier M, Wolff H, Schwarz HP, Quinkler M, Beuschlein F, Reincke M. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2009; 94:1665–1670.
12. Ashley RA, McGee SM, Isotaolo PA, Kramer SA, Cheville JC. Clinical and pathological features associated with the testicular tumor of the adrenogenital syndrome. *The Journal of urology*. 2007;177(2):546–549.
13. New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, Sun L, Zaidi M, Wilson RC, Yuen T. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. *Proc Natl Acad Sci USA*. 2013; 110:2611–2616.
14. Claahsen-van der Grinten HL, Hermus AR and Otten BJ. Testicular adrenal rest tumors in congenital adrenal hyperplasia. *Int J Pediatr Endocrinol* 2009; 2009:624823.
15. Wilkins L, Fleishmann W, Howards JE. Macrogonitosomia precox associated with hyperplasia of the androgenic tissue of the adrenal and death from corticoadrenal insufficiency. *Endocrinology* 1940; 26:358–395.
16. Bonaccorsi AC, Adler I, Figueiredo JG. Male infertility due to congenital adrenal hyperplasia: testicular biopsy findings, hormonal evaluation, and therapeutic results in three patients. *Fertil Steril*. 1987; 47(4):664–70.
17. Giacaglia LR, Mendonca BB, Madureira G, Melo KF, Suslik CA, Arnhold IJ, Bachega TA. Adrenal nodules in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: regression after adequate hormonal control. *J Pediatr Endocrinol Metab*. 2001; 14(4):415–419.
18. Murphy H, George C, de Kretser D, and S. Judd S. Successful treatment with ICSI of infertility caused by azoospermia associated with adrenal rests in the testes. *Hum Reprod*. 2001; 16(2):263–267.
19. Walker BR, Skoog SJ, Winslow BH, Canning DA, Tank ES. Testis sparing surgery for steroid unresponsive testicular tumors of the adrenogenital syndrome. *J Urol*. 1997; 157(4):1460–1463.
20. Zimmermann A. New Molecular and Metabolic Aspects in Romanian Patients with Classic 21-Hydroxylase Deficiency. *Acta Endocrinolog (Buc)*. 2012; 8(3):471–478.
21. Meng X, Yu Y. Nonclassical 21-Hydroxylase Deficiency Presented As Addison's Disease and Bilateral Adrenal Incidentalomas. *Acta Endocrinolog (Buc)*. 2017; 13(2):232–236.
22. Jaresch S, Kornely E, Kley HK, Schlaghecke R. Adrenal incidentaloma and patients with homozygous or heterozygous congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1992; 74:685–689.
23. Nermoen I, Rorvik J, Holmedal SH, Hykkerud DL, Fougner KJ, Svartberg J, Husebye ES, Løvås K. High frequency of adrenal myelolipomas and testicular adrenal rest tumours in adult Norwegian patients with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Clin Endocrinol (Oxf)*. 2011; 75: 753–759.
24. Sakaki M, Izaki H, Fukumori T, Taue R, Kishimoto T, Kanayama HO. Bilateral adrenal myelolipoma associated with adrenogenital syndrome. *Int J Urol*. 2006; 13(6):801–802.
25. Plaut A. Myelolipoma in the adrenal cortex; myeloidipose structures. *Am J Pathol*. 1958; 34(3):487–515.