

Three Cases of Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia—A Diagnostic and Therapeutic Challenge



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CASE 1

A 23-year-old man presented with massive enlargement of his testes. He had a known history of salt-wasting congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) and was on glucocorticoid and mineralocorticoid replacement since initial diagnosis at birth with a current treatment regimen of prednisolone 7.5 mg and fludrocortisone 75 μ g daily. However, compliance was poor as reflected by hormonal control parameters out of target range (Table 1). Ultrasound of the testes revealed the presence of massive bilateral tumors with mixed hypo- and hyperechogenic appearance. An additional semen analysis revealed azoospermia. Magnetic resonance imaging (MRI) confirmed bilateral testicular tumors (12 mL right, 9.6 mL left; Fig. 1A).

An intensified glucocorticoid treatment was initiated with addition of night time dexamethasone administration (initially 2.5 mg/d) to his regular substitution therapy with prednisolone (7.5 mg/d) and fludrocortisone (0.075 mg/d). Dexamethasone dosage was tapered off to 0.5 mg given at night time over a period of 5 months. At follow-up examination after 6 months, the patient's hormone profile significantly improved (Table 1) with normal baseline adrenocorticotropic (ACTH, 12 pg/mL), slightly elevated 17-alpha-hydroxyprogesterone

(17-OHP, 6.2 ng/mL), androstenedione of 0.4 ng/mL, testosterone of 322 ng/dL, and normalized luteinizing hormone (LH; 9.5 U/L) and follicle stimulating hormone (FSH) concentrations (5.4 U/L). In line with the improvement of hormonal follow-up parameters, MRI showed significant reduction of testicular tumor size from an initial total tumor volume of 22.8 mL (3.9 right testis, 4.1 left testis; Fig. 1B). Furthermore, azoospermia resolved with a sperm count of 2.5 million/mL.

CASE 2

A 30-year-old man presented with bilateral inguinal pain radiating to the genitals. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) had been diagnosed shortly after birth. Due to continuous glucocorticoid replacement, infancy and adulthood were uneventful with normal growth and pubertal changes. At the age of 20 years, the patient was diagnosed with bilateral testicular masses when explorative surgery and percutaneous biopsies were performed at an external urology department. The biopsies showed a nodular hyperplasia of eosinophilic cells in the rete testis and the testicular stroma. Five years later, another 2 biopsies of the testis were taken due to testicular enlargement and pain. The patient stated that he fathered a daughter at 26 years.

When the patient presented at our clinic, his actual medication consisted of 30 mg hydrocortisone daily. On physical examination the testis were tender, normal in size (left 15 mm, right 18 mm), and a mass was palpable on the right testis. Laboratory data showed normal serum electrolytes, grossly elevated 17-OHP (138 ng/mL), normal testosterone, FSH, and luteinizing hormone levels. Alpha-fetoprotein and β -human chorionic gonadotropin were within normal range. ACTH levels were significantly elevated in the morning hours but within the normal range from 12 PM to 2 PM (Fig. 2). Scrotal ultrasonography showed a mass of 2 \times 1.8 cm at the upper part of the right testis and multiple small nodules in both

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Table 1. Clinical and laboratory features before and 6 months after treatment intensification (case 1).

| | Baseline | 6 Months | Normal Values |
|----------------------------------|----------------------------------------------|---------------------------------------------|---------------|
| Plasma ACTH (pg/mL) | 62 | 12 | 5-60 |
| 17-OHP (ng/mL) | 343 | 6.2 | 0.4-3.3 |
| Androstenedione (ng/mL) | >7.4 | 0.4 | 1.2-4.8 |
| Testosterone (ng/dL) | 624 | 322 | 350-900 |
| LH (U/L) | <1.0 | 9.5 | 1.0-10.0 |
| FSH (U/L) | <1.0 | 5.4 | 1.0-10.0 |
| MRI tumor size (mL) | Right testis: 12.0 mL Left testis: 9.6 mL | Right testis: 3.9 mL Left testis: 4.1 mL | |
| Sperm count ($\times 10^6$ /mL) | <0.1 (azoospermia) | 2.5 | >39 |

ACTH, adrenocorticotropic hormone; FSH, follicle stimulation hormone; LH, luteinizing hormone; MRI, magnet resonance imaging; 17-OHP, 17-hydroxyprogesterone.

testes. A semen analysis showed no vital spermatocytes. To suppress elevated ACTH levels in the early morning hours, dexamethasone (0.25 mg at night) was added to the glucocorticoid replacement therapy and the hydrocortisone dose was reduced to 15 mg daily. This leads to an effective reduction of ACTH concentrations particularly in the morning hours (Fig. 2). A follow-up examination

2 years later showed a normal ACTH concentration at 20:00 (6 pg/mL). The testis were soft and indolent, on ultrasound examination, the right-sided mass had shrunk to 1.2×1.2 cm, while the other nodules were smaller and less in number.

CASE 3

A 35-year-old man was evaluated for infertility at an external urology department. CAH due to 21-hydroxylase deficiency had been diagnosed based on clinical and biochemical findings in the neonatal period. For treatment of CAH, the patient had been taken 0.25 mg dexamethasone per day for 16 years. Because of increased appetite and consequently significant weight gain, he had refused adequate glucocorticoid replacement therapy. Throughout childhood, CAH was also poorly managed. According to the patient and his medical records, the patient experienced repeated adrenal crisis requiring emergency hospitalization. He underwent a precocious puberty at the age of 8 years with accelerated skeletal maturation and reached a final height of 153 cm (below 5th percentile). Current urologic examination revealed bilateral small and hard testes. Electrolytes, alpha-fetoprotein, β -human chorionic gonadotropin were normal, serum free testosterone was low (1.2 pg/mL; NR 9-47 pg/mL). Scrotal ultrasonography showed bilateral small testes (right 5.8 mL, left 6.2 mL) with decreased echogenicity and heterogeneous pattern. Percutaneous testicular biopsy was performed for histopathologic evaluation. As malignancy of the testicular tumors could not be ruled out and sonographically and microscopically nearly no functional testicular tissues were left, bilateral orchiectomy was performed. Gross pathologic evaluation of the surgical specimen showed bilateral multifocal nodular masses in the testis, rete testis, and spermatic cord. Histopathologic examination of the formalin-fixed testicular tissue showed numerous paratesticular nodules consisting of large, polygonal, eosinophilic cells separated by fibrous stroma (Fig. 3A) and few atrophic seminiferous tubules lined by Sertoli cells only and no spermatogenic cells. No Leydig cells were found in the interstitium. The tumor cells contained a brown lipochrome pigment (Fig. 3B), Reinke crystalloids were not identified. On physical examination the patient was obese

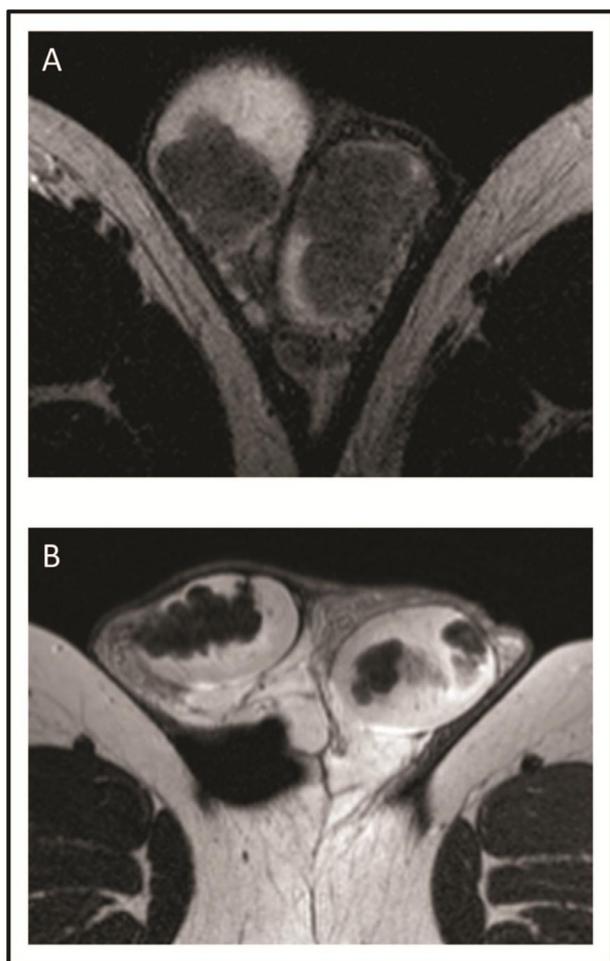


Figure 1. T2-weighted axial images of dedicated testicular magnetic resonance imaging (MRI). Extensive hypointense cauliflower-like mass within both hyperintense testis before (A) and reduction of bilateral mass 6 months after treatment (B) (case 1).

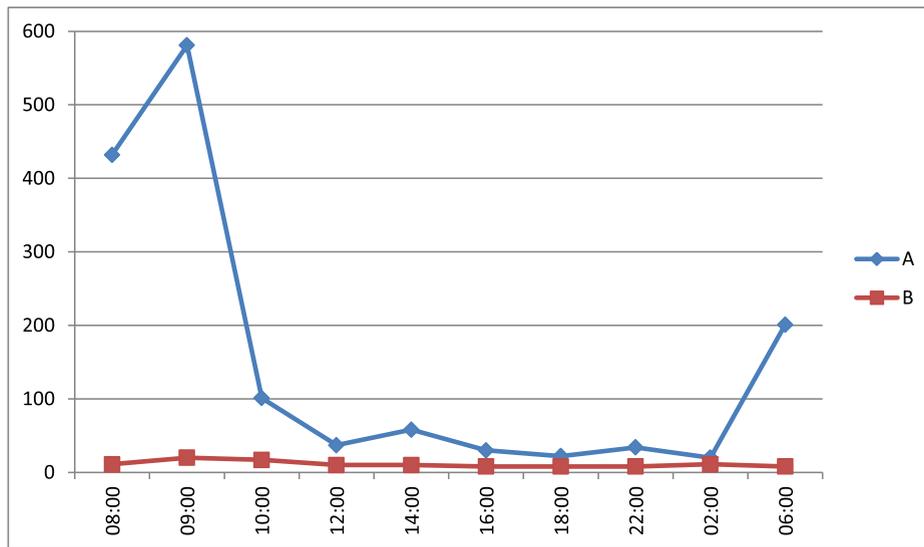


Figure 2. ACTH levels before and after treatment intensification (case 2). (A) Treatment with 30 mg hydrocortisone in the morning (7 AM); (B) treatment with 15 mg hydrocortisone in the morning and 0.25 mg dexamethasone at night (10 PM); ACTH, adrenocorticotropic hormone (normal range: 5-60 pg/mL). (Color version available online.)

(75 kg, body mass index (BMI) 32) with pigmentation of palmar creases and scars. The remainder of examination was normal. LH and FSH were suppressed (both 0.2 U/L), plasma ACTH and 17-OHP concentrations were highly elevated (ACTH 1327 pg/mL; 17-OHP 42 ng/mL). The

patient was placed on hydrocortisone 15 mg/day, dexamethasone 0.5 mg/at bedtime, and fludrocortisone 0.1 mg/day. At follow-up (12 months after first evaluation), plasma ACTH and renin concentrations were only slightly elevated. No adrenal rest tumors reoccurred after orchiectomy.

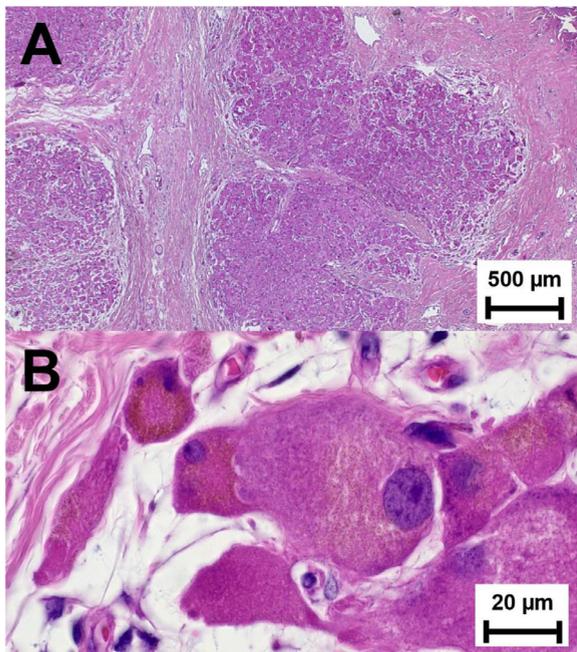


Figure 3. Histopathologic examination of surgical specimen (case 3). (A) (hematoxylin and eosin, $\times 10$) Microscopic view of the tumorous testis. The cells grow in nodules separated by fibrous septa. (B) (hematoxylin and eosin, $\times 40$) The cells are polygonal with considerable nuclear variability and abundant eosinophilic cytoplasm which partially contains a large amount of brown lipochrome pigment. (Color version available online.)

DISCUSSION (NICOLE REISCH, M.D.)

CAH due to 21-hydroxylase deficiency is an inherited metabolic disorder affecting approximately 1 in 15,000 individuals.¹ Complex dysfunction of adrenal steroid synthesis leads to glucocorticoid—and in the salt wasting form mineralocorticoid—deficiency with compensatory high concentrations of ACTH, hypertrophy of the adrenal glands and subsequently accumulation of precursor hormones and adrenal sex steroids.¹ Treatment of CAH consists of glucocorticoid and, in the case of salt wasting, mineralocorticoid replacement and is sometimes not easy to achieve as it is extremely hard to strike the balance between over- and undertreatment. Long-term complications range from glucocorticoid side effects to poorly controlled adrenal androgen excess.¹ An important complication in adulthood is infertility—in male patients mainly caused by hypogonadotropic hypogonadism (due to the excess of adrenal androgens being aromatized to estrogens suppressing the gonadotrophins) and testicular adrenal rest tumors (TARTs).^{1,2}

TARTs are located in the rete testis and considered to develop from aberrant adrenal cells which become hyperplastic under continuous stimulation of ACTH.³ Depending on the screening method and patient selection, TARTs can be found in a varying percentage (0%-94%) of male patients with CAH.^{3,4} Clinical diagnosis of testicular masses can be made by palpation of testis, which in

case of TARTs often shows their bilateral affection. Small TARTs might be overseen in clinical examination; therefore, imaging of the testes by ultrasound or MRI should be performed. Both methods were shown to be equally useful in the diagnostic of TART while ultrasound is cheaper but more dependent on the investigator's experience.⁵ On ultrasound small TARTs (<2 cm) often appear hypoechoic, while larger lesions (>2 cm) are of mixed echogenicity with hypo- and hyperechoic reflections as in case 1.⁵ Typical MRI features are isointense appearance on T1-weighted and hypointense appearance on T2-weighted images, while tumor margins are usually well defined (see Fig. 1).⁵ We chose to additionally use MRI in this case to document the therapeutic effect independent from the investigators' experience and interinvestigator variance.

Adequate laboratory work-up is important when evaluating patients with TARTs. TARTs are always benign, whereas Leydig cell tumors (LCT) can follow a malignant course. Some patients still undergo unnecessary testicular surgery because of suspected malignancy.⁴ In case 3, orchiectomy was performed without prior endocrine evaluation. Histology in this patient revealed typical features of TARTs and no sign of malignancy (Fig. 3). Findings in testicular biopsy can sometimes be misleading with characteristics of LCT as they are histologically quite similar to TARTs. Also clinically it can be challenging to distinguish TARTs from LCTs, which account for less than 3% of testicular tumors.⁶ Unlike TARTs histopathology of LCT reveals specific Reinke crystalloids in about 25%-40%, but their absence does not rule out LCT. When distinguishing between TART and LCT, the following features make diagnosis of TART more likely: young age, bilateral presence of tumors, history of poor therapeutic compliance, and absence of metastasis.^{6,7} Most importantly, one has to be aware of the fact that the patient has CAH: whereas TARTs occur in a high percentage of CAH patients, LCTs in CAH patients have rarely been described.^{8,9} Most importantly, TART can decrease in size under adrenal-suppressive dexamethasone therapy. Therefore, it is important to document the number and location of TART. Diagnostic biopsies in patients with TARTs are usually not necessary and should only be performed in cases with a suspicion for LCT. The only indication for surgery in TART is the relief of pain and discomfort by large TART. After careful history, physical examination, biochemistry, and imaging, a tumor biopsy and additional functional data as gonadal vein blood sampling can ensure the diagnosis prior to most likely unnecessary orchiectomy with far-reaching consequences for the patient.⁷ Our patient in case 2 underwent multiple testicular biopsies and even explorative testicular surgery prior to presentation at our clinic. Biopsies showed features of TART tissue which also could have been mistaken for LCT and finally could have led to bilateral orchiectomy. Interestingly, the patient told our team that he had fathered a child even after testicular biopsies and explorative surgery. With the history of recurring TARTs and

semen analysis with no vital spermatocytes fatherhood remains highly questionable. Due to ethical reasons, no genetic testing was performed.

TART may reduce in size by effective adrenal suppression with dexamethasone.^{10,11} High levels of ACTH and 17-OHP as marker of inadequate glucocorticoid treatment were present in all our 3 patients. In case 2, high ACTH particularly in morning hours suggested inadequate treatment during the night. In the other patients (cases 1 and 3), poor compliance was apparently the reason for the displaced hormone values. Noncompliance probably plays a major role in TART growth and has often been reported in literature.⁷ Therefore, first treatment goal should be ensuring patient's compliance. Controversially association of hormonal control with TART presence or size could not be demonstrated so far.¹² Additionally, there are reports of patients with TARTs despite of good disease control of their CAH, arguing other growth stimulating factors.^{13,14} Angiotensin II receptors were found in TART tissue supporting growth stimulation in patients with insufficient mineralocorticoid treatment; therefore, additional mineralocorticoid treatment should even be contemplated in patients with simple virilizing CAH.¹⁵ Renin was elevated in case 3, therefore, mineralocorticoid treatment presumably was inadequate. This additionally might have aggravated growth of patient's TARTs.

As endocrine disease control turned out to be poor in all cases, dexamethasone was added to the patients' medication. In case 1, dexamethasone was added at a dosage of 2.5 mg which indeed seems to be high and a lower dose is likely to have been sufficient. Other authors suggest switching hydrocortisone to an equivalent daily dose of dexamethasone.¹⁰ However, in this patient, a relatively high initial dose was chosen to further substantiate the diagnosis of TART with glucocorticoid dependent rapid tumor mass reduction. Moreover, dexamethasone dosage was rapidly reduced to 0.5 mg. In the other patients, daily glucocorticoid doses of 0.25 mg dexamethasone and 15 mg hydrocortisone (case 2) and 0.5 mg dexamethasone additional to 15 mg hydrocortisone (case 3) were chosen and proved to be effective concerning patients' endocrine disease control.

TARTs are not malignant but can do severe and even irreversible testicular damage by compression of the seminiferous tubules and toxic paracrine effects.¹⁶ Thus, semen analysis should be performed to evaluate fertility. It is reported that only 24% of male CAH patients have normal semen quality.¹⁷ Based on recent Swedish population-based data, fertility rates in male CAH are diverse with reduced number of biological children suggesting impaired fertility, but also normal fertility in some subgroups.¹⁸ Impaired sperm production in patients with CAH is not only caused by TARTs but also hypogonadotropic hypogonadism with LH and FSH being suppressed due to increased aromatization of androgens.² Assessing biochemically gonadal function can be challenging in CAH patients as it is impossible to distinguish testosterone of testicular and adrenal origin.

Testosterone, LH and FSH are influenced by the disease and/or its treatment as shown in our case descriptions. In poor disease control testosterone of adrenal origin increases and suppresses the hypothalamus-pituitary-gonadal axis (via conversion to estradiol). Intensifying disease control by adrenal suppressive therapy with dexamethasone leads to a decline of testosterone concentrations as testosterone of adrenal origin decreases as shown in case 1. In ambiguous situations, it may be useful to measure Inhibin B in CAH patients as it seems to be a good marker for Sertoli cell function,² taking the androstenedione to testosterone ratio helps to distinguish the adrenal vs the testicular source of testosterone.¹⁹

In advanced stages of TARTs, sometimes adequate glucocorticoid treatment shows no effect. If so, surgery should be considered and testicular biopsy can be useful to evaluate reversibility of infertility.³ Testis-sparing surgery can be offered in cases of ineffective glucocorticoid treatment and absent irreversible damage in histology.¹⁶ Testicular damage due to fibrosis and lymphocytic infiltration might be irreversible and surgery therefore not effective in restoring fertility or improving gonadal dysfunction.³

In conclusion, TARTs are an important complication of CAH, possibly leading to infertility. Thus, early recognition, diagnosis, and treatment of TARTs are crucial for a better prognosis of fertility. Conservative treatment by adrenal suppressive glucocorticoid therapy can be effective even in massive TARTs (case 1). These testicular tumors have prompted biopsies (case 2) and sometimes even orchiectomy (case 3). Therefore, an important fact in the diagnostics of TART is to appreciate the circumstance that the patient has CAH. If a patient with diagnosis of testicular masses—or even LCT in a testicular biopsy—raises the suspicion of undiagnosed CAH, an endocrinologist should be involved. Key objective remains a multiprofessional collaboration of endocrinologist, urologist, and radiologist who are involved in diagnosis and treatment of CAH patients. Because many patients with TARTs show poor compliance, regular follow-up should be carried out by this multiprofessional team.

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