# Testicular adrenal rest tumors (TARTs) as a male infertility factor. Case report

## Testicular adrenal rest tumors (TARTs) jako czynnik niepłodności męskiej. Opis przypadku

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### Abstract

*Since testes and adrenal cortex derive from the same urogenital ridge, adrenal tissue with descending gonads may migrate in early embryonic period. Although most often ectopic tissue undergoes atrophy, in some cases, when adrenocorticotrophic (ACTH) overstimulation occurs, the adrenal remnants in the testes may become hypertrophic and form testicular adrenal rest tumors (TARTs). The growth of TARTs in the testes leads to obstruction of the seminiferous tubules which can mechanically impair the function of the gonads and cause irreversible azoospermia.*

*We describe a patient suffering since neonatal period from congenital adrenal hyperplasia (CAH), disorder with defected pathway of cortisol production, which leads to increased ACTH production and to overstimulation of adrenal cortex. He had very poor disease control and therefore in late puberty he was diagnosed with TARTs. At the age of 19.5 he was diagnosed with azoospermia, most likely caused by TARTs.*

*It is the first evidence of TARTs in Polish literature. Although not many cases have been published so far, the incidence of TARTs seems to be highly underdiagnosed, so it seems reasonable to consider the disease in differential diagnosis of male infertility.*

Keywords: **male infertility**/ **azoospermia**/ **TARTs**/ / **testicular adrenal rest tumors** /

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**Streszczenie**

*Zarówno jądra jak i nadnercza wywodzą się z parzystych grzebieni moczowo-płciowych. Fragmenty tkanki kory nadnerczy mogą we wczesnym okresie rozwoju embrionalnego migrować wraz z gonadami do moszny. W większości przypadków ektopowa tkanka nadnerczowa zanika, jednak u pacjentów z wysokim poziomem hormonu adenokortykotropowego (ACTH) może ona ulegać rozrostowi i tworzyć w jądrach guzy – testicular adrenal rest tumors (TARTs). Ich wzrost prowadzi do obstrukcji kanalików nasiennych, co upośledza funkcję jąder i może powodować nieodwracalną azoospermię.*

*W pracy przedstawiono pacjenta chorującego od urodzenia na wrodzony przerost nadnerczy (congenital adrenal hyperplasia – CAH) związany z upośledzoną produkcją kortyzolu i zwiększonym wydzielaniem ACTH. Pacjent nieregularnie poddawał się zalecanemu leczeniu i stąd w okresie dojrzewania zdiagnozowano u niego TARTs, zaś w wieku 19,5 lat całkowity brak nasienia.*

*Pacjent z TARTs został opisany przez nas po raz pierwszy w polskiej literaturze. Choć nie publikowano dotąd wielu opisów przypadków tej choroby, wydaje się, że jest ona zbyt rzadko rozpoznawana. TARTs powinno być zawsze brane pod uwagę w diagnostyce różnicowej męskiej niepłodności.*

Słowa kluczowe: **niepłodność męska** / **azoospermia** / **TARTs** / / **testicular adrenal rest tumors** /

## Introduction

Testes and adrenal cortex both derive from the same urogenital ridge. Therefore, in early embryonic period, adrenal tissue with descending gonads may migrate, which is the case in 7.5-15% of male newborns [1]. In most cases these ectopic fragments undergo atrophy in the early childhood. Adrenal tissue remnants do not affect testes unless there is adrenocorticotrophic hormone (ACTH) overstimulation. High levels of ACTH may lead to hyperplasia of adrenal fragments in gonads, which might generate the formation of testicular adrenal rest tumors (TARTs) [2].

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders with a deficiency of enzymes necessary for normal physiological pathway of cortisol production. Cortisol deficiency leads to an increased ACTH production and to an overstimulation of the adrenal cortex in which case adrenal hyperplasia occurs. TARTs are present in 50-94% of the male patients suffering from CAH [3]. They are usually found bilaterally and they are never malignant. While the tumors are mainly located in the mediastinum of the testis, they can affect male fertility [4]. The growth of TARTs may lead to obstruction of the seminiferous tubules and anatomically impair the function of the testis. Long-lasting compression of testicular tissue may cause irreversible azoospermia [4]. Moreover, it is hypothesized that TARTs may have endocrine activity and produce androgens, which in turn may reduce the efficacy of hormonal substitution therapy in CAH patients, thus causing additional problems in fertility [5].

We describe a patient suffering from CAH since neonatal period with TARTs, diagnosed late in puberty, which negatively affected his fertility in the adulthood.

### *The patient*

The male patient was born in 1990. He was diagnosed with a classical salt-wasting CAH (21-hydroxylase deficiency) in the first weeks of his postnatal life. He has been under medical observation in Department of Pediatric Endocrinology and Rheumatology of Karol Jonscher's Clinical Hospital of Poznan University of Medical Sciences Poland and in pediatric endocrine outpatient clinics of the Hospital. He received hydrocortisone plus fludrocortisone treatment, but therapy had never been regular.

At the age of 17.5 years, 2 years after his last visit, a bilateral increased density of the testes was confirmed on palpation. Ultrasonography revealed well bordered, hypoechogenic, heterotrophic multifocal masses which covered the volume of one third to half of both testes. Similar changes were also noticed along spermatic cords which were widened. The previous ultrasonographic examinations performed at the age of 12 and 15 years were normal. Neoplastic tumor markers (CEA, AFP and β-hCG) were normal, thus excluding malignant process in the gonads. The patient was diagnosed with TARTs. He had very poor disease control [17α-OH-progesterone 30.7 ng/ml (N: 0.32-3.30), androstendione 12.1 ng/ml (N: 0.1-0.9)]. Afterwards he promised to take medications (hydrocortisone) according to prescribed formula and 2 weeks later his ACTH was 14.8 pg/ml (N: 10-60), 17α-OH-progesterone 2.60 ng/ml, androstendione 1.1 ng/ml and DHEA-S 1.91 μmol/l. With an adequate treatment, the disease control was perfect. LH was 6.7 mIU/ml (N: 2.0-12.0), FSH 10.9 mIU/ml (N: 1.0-8.0) and testosterone 9.73 nmol/l (N: 8.20-34.6).

3 months later his FSH level increased to 12 mIU/ml and LH to 10.9 mIU/ml. Testosterone increased to 15.9 nmol/l. Magnetic resonance imaging (MRI) showed hypointensive areas adjacent to testicular vessels and plexus pampiniformis in both testes. MRI confirmed the diagnosis of TARTs.

Two years later, at the age of 19.5 years, the patient's semen sample was examined separately two times and azoospermia was evidenced. Even with adequate treatment the gonadal ultrasound still showed the presence of hypoechogenic lesions comparable to the previous ultrasound (Figure 1a - right testis and Figure 1b - left testis). and MRI examinations, indicating that the changes in gonads were irreversible.

## Discussion

TART is classically associated with a poorly-controlled CAH, a salt-wasting form. However, it may also be found in patients with other diseases with increased ACTH level, such as Cushing's disease and Nelson's syndrome [6]. Moreover, if the volume of adrenal remnants which migrate to gonads is large, then TARTs may also develop in patients with a moderately elevated ACTH level, such as simple-virilizing CAH or in late-onset CAH. [5] Infertility caused by TART may be the

first finding in these patients. As mentioned, the prevalence of ectopic adrenal tissue in early infancy is relatively high. Also, the incidence of CAH is 1:10000-12000 live births, so it seems reasonable to consider TARTs in differential diagnosis of azoospermia.[7]

To the best of our knowledge, it is the first evidence in Polish literature that TARTs may influence male fertility. It has to be underlined that although not many cases have been published so far, the incidence of TART seems to be highly underdiagnosed. It is important to stress that not only in women but also in men congenital anomalies of the reproductive tract can have a tremendous effect upon future fertility. [8-9] TART has to be taken into account in diagnostics and treatment of male infertility. Late finding of TART and inappropriate or not definitive therapy may lead to obstructive azoospermia, like in the patient described above.

No standard treatment of TARTs and associated with infertility has been published so far. Some authors achieved good results with adequate steroid treatment. Claahsen-van der Grinten et al. presented a case report of a patient with bilateral TART and azoospermia, in whom hydrocortisone was replaced by dexamethasone and lead to reduction of the tumor size. [10] After such a treatment , semen parameters had improved, which allowed the couple a spontaneous conception. Although infertility has been treated, that patient suffered from severe weight gain and the presence of striae after high-dose glucocorticoid therapy. [10] Surgical therapy is not recommended since the outcome is poor, especially in cases of long-standing bilateral TARTs [11] Since the damage in gonadal tissue due to TARTs is irreversible and the tumors are mainly located in the mediastinum of the testis, it seems that assisted reproductive technologies may be helpful in conceiving the child in these patients. [12] The biopsy of the testis performed from the periphery, not affected by TART tissue, gives the chance to obtain sperms able to fertilize the oocyte in ICSI (intracytoplasmatic sperm injection) procedure.

To sum up, the authors address this educational paper to all physicians dealing with reproductive medicine. High incidence of TARTs, mostly in CAH patients (also in late-onset subjects), should always be considered in the diagnostic work-up and treatment modality of impaired semen parameters and azoospermia.

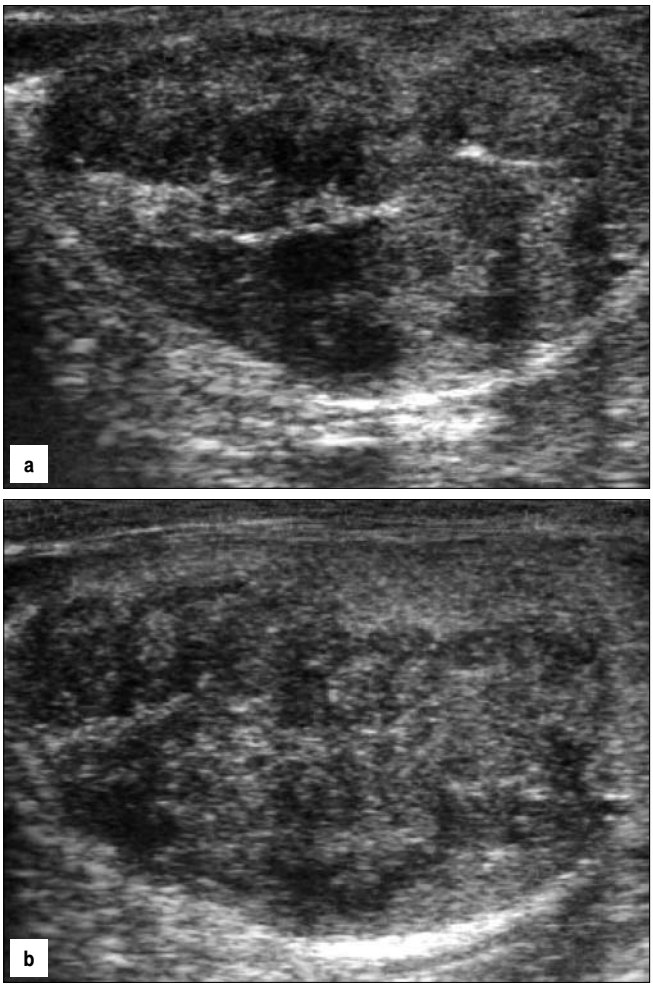


**Figure 1a-b.** Bilateral testicular adrenal rest tumors shown by ultrasound: 1a – right testis, 1b – left testis.

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