

Beyond malignancy: recognising testicular adrenal rest tumours

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Background: Testicular adrenal rest tumours (TART) are sporadic testicular masses mainly occurring in individuals with congenital adrenal hyperplasia (CAH) due to stimulation by adrenocorticotrophic hormone (ACTH).^{1,2} If not detected early, these masses can lead to testicular dysfunction and infertility.^{1,3} This report presents two cases of TARTs, one in a child and another in an adult, highlighting differences in clinical presentation, diagnostic challenges, and management approaches.

Methods: Both cases with established CAH presented with testicular masses, which were diagnosed through a combination of clinical evaluation, hormonal profiling, and testicular ultrasound. Management focused on optimisation of glucocorticoid therapy and regular follow-up to monitor tumour progression and prevent unnecessary surgical procedures.

Results: In both cases, TARTs were confirmed. The paediatric patient had an early-stage TART with preserved testicular function, whereas the adult patient exhibited impaired testicular function with elevated ACTH levels. Following improvement in glucocorticoid therapy, the paediatric patient showed a decrease in tumour size, while the adult patient showed a stable tumour size with no further decline in testicular function. Surgical intervention was not required for either patient, emphasising the significance of early diagnosis and management in preventing long-term complications.

Conclusion: Early detection and optimised glucocorticoid therapy are critical in managing TARTs in CAH. Well-timed intervention can protect testicular function and prevent complications, emphasising the need for regular monitoring and clinical awareness.

Keywords: testicular adrenal rest tumours, malignancy

Introduction

Testicular adrenal rest tumours (TARTs) are sporadic, benign masses originating from ectopic adrenal tissue in the testes, initially reported by Wilkins et al.⁵ in 1940.^{1,4} Because of their morphological and physiological similarity to adrenal tissue, these masses are referred to as “testicular adrenal rest tumours”.^{1,6} TARTs are mostly present in males with congenital adrenal hyperplasia (CAH), usually due to 21-hydroxylase deficiency (21-OHD) (90–95%).^{2,4,7} Deficient cortisol production results in increased adrenocorticotrophic hormone (ACTH) stimulation, causing precursors of hormones to become testosterone, which, in addition to premature puberty, causes hyperplasia of ACTH-sensitive tissue, such as the testicles.^{3,8} This hormonal imbalance promotes the development of TARTs, which occur in up to 94% of adult men with CAH.⁴ Prevalence varies depending on age. Among patients under 18, prevalence rates of 24–29% have been reported, with an increase during puberty.^{1,9,10-12}

Regular monitoring of ACTH and related hormones is essential to ensure effective hormonal control.⁷ Ultrasound imaging helps

detect testicular masses early and distinguishes TARTs from Leydig cell tumours (LCT), which share similar symptoms, like testicular enlargement and infertility.^{7,8} In longstanding cases, a testicular biopsy is essential to evaluate the residual testicular parenchyma, as TARTs can cause obstruction along with loss of germ and Sertoli cells.^{1,2}

TART management in CAH involves optimising glucocorticoid therapy to control tumour growth and preserve fertility.¹ Surgery is considered if hormonal therapy fails, especially in advanced stages (Stage 3 and beyond).^{1,13,14} Testis-sparing surgery may help, but it lacks long-term data.¹ Fertility counselling and early semen cryopreservation are recommended when complete prevention is impossible.^{1,15}

Case presentations

Case 1 describes a 15-year-old male, diagnosed with salt-wasting CAH due to 21-OHD, who presented to the urology clinic with painless bilateral testicular enlargement. The patient had been



Figure 1: Ultrasound of the testes demonstrating bilateral hypoechoic lesions with bilateral microlithiasis

diagnosed in infancy following a salt-wasting crisis. Throughout childhood and adolescence, his inconsistent adherence to steroid replacement therapy resulted in inadequate hormonal control, with persistently elevated 17-hydroxyprogesterone (17-OHP) levels ranging from > 109 µg/L at age seven to 639 µg/L by age 13.

During the examination, he appeared to be overdeveloped for his age, with pubic hair already at Tanner stage III, penis enlargement, and advanced bone age. The initial ultrasound (Figure 1) showed bilateral testicular microlithiasis and hypoechoic, hypervascular lesions in both testes. Follow-up imaging six months later confirmed persistent microlithiasis and stable testicular lesions with mild testicular enlargement. No new masses were detected, and the epididymis appeared normal.

Case 2 involves a 35-year-old male with salt-wasting CAH due to 21-OHD, diagnosed neonatally. Initial treatment with corticosteroids corrected severe electrolyte imbalances. Early therapy adherence led to biochemical stabilisation; however, from age eight, poor compliance caused hormonal dysregulation and premature skeletal maturation by age 14. At this time, ultrasound and hormone levels suggested bilateral TARTs with increased testicular volumes. Testicular masses showed minimal progression, and subsequent imaging revealed hydroceles and adrenal enlargement.

Corticosteroid therapy was adjusted over time, including a dose reduction at age 28 due to subclinical Cushingoid features. Irregular medication use, particularly during shift work, continued to affect hormonal control. At age 33, abnormal testicular ultrasound findings were concerning for malignancy; however, given the clinical context

and sonographic features in keeping with bilateral TARTs, a biopsy was omitted (Figure 2).

The patient resumed endocrine management with stable prednisolone and fludrocortisone therapy, maintaining normal electrolytes and improved testosterone levels. However, 17-OHP remained markedly elevated (from 71.4 µg/L at age 14 to 4 861 µg/L in adulthood) due to inconsistent treatment adherence. The interval testicular ultrasound after two years demonstrated unchanged testicular lesions (Figure 3).

Discussion

TARTs in CAH patients, particularly those with 21-OHD, are well-documented complications, but their clinical progression and management remain challenging.¹ The cases presented provide insight into the clinical course, pathophysiology, and management strategies for CAH-associated TARTs, helping to understand the disease and its complications better.¹ However, the progression of these tumours and their impact on fertility remain less explored.¹

Clinical evidence suggests that while high doses of glucocorticoids can shrink tumours by inhibiting ACTH release, tumour growth may accelerate when ACTH levels rise, as seen in poorly managed CAH.^{1,16} This suggests that tumour cells possess ACTH receptors, and that TARTs may originate from adrenal cells that migrated to the testes during embryonic development.^{1,7} In both cases, the sustained elevation of 17-OHP due to non-optimised glucocorticoid therapy likely contributed to persistent ACTH secretion.

Hormonal dysregulation results in both hyperandrogenaemia and the stimulation of ectopic adrenal tissue in the testes, ultimately leading to TART development.¹ In case 1, poor medication adherence and fluctuating cortisol and mineralocorticoid levels probably prevented effective ACTH suppression. In case 2, the interruptions due to shift work likely led to insufficient suppression of adrenal androgens, creating an environment conducive to the growth of testicular adrenal remnants.

The delayed TART diagnoses in both cases may be due to the subclinical nature of early adrenal rest tissue growth.^{1,7} Earlier detection might have been possible with more aggressive monitoring, including early imaging and hormonal assessments. In case 2, imaging revealed bilateral TARTs and increased testicular volumes, with minimal tumour growth seen on follow-up ultrasound after treatment optimisation. Pharmacological management with betamethasone and fludrocortisone led to tumour regression. This case highlights the importance of individualised glucocorticoid therapy and regular monitoring to control adrenal hyperstimulation, prevent TART progression, and preserve testicular function.

Differentiating TARTs from LCTs can be challenging, as both present as testicular masses linked to early puberty and infertility.^{7,8} LCTs with malignant potential are the most critical differential diagnosis, making accurate distinction vital for proper management.^{8,17} Histological differentiation between TARTs and LCTs is often difficult.⁷ However, certain clinical characteristics can aid in distinguishing these two: TARTs occur bilaterally in over 80% of cases, whereas LCTs only occur bilaterally in about 3%. Furthermore, Reinke crystals, which

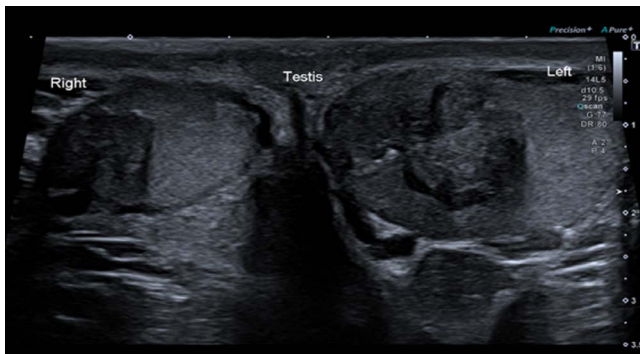


Figure 2: Ultrasound of the right testis demonstrating a heterogeneous, mixed, solid and cystic mass with microlithiasis

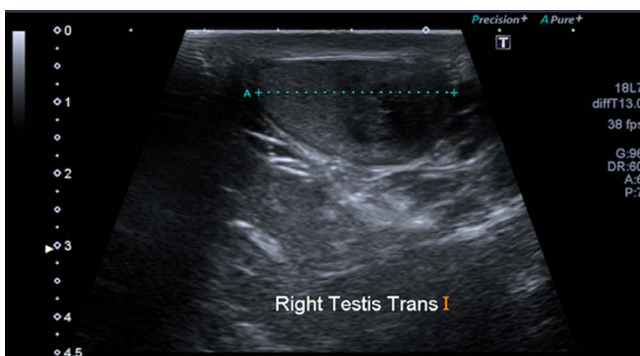


Figure 3: Ultrasound of the testes demonstrating unchanged bilateral testicular masses

	Histological description	Reversibility	Treatment options
Stage 1	Presence of adrenal rests within the rete testis (not detectable)	+++	—
Stage 2	Hypertrophy and hyperplasia of adrenal rest cells due to growth-stimulating factors (e.g. ACTH, AII)	+++	Optimising glucocorticoids
Stage 3	Further growth of the adrenal rest cells with (reversible) compression of the rete testis	++	Optimising glucocorticoids Surgery?
Stage 4	Induction of fibrosis and focal lymphocytic infiltrates	-/+	Surgery?
Stage 5	Part of the tumour is replaced by adipose tissue	-	—

Figure 4: Proposed classification of TARTs¹

ACTH – adrenocorticotropic hormone, AII – Angiotensin II, TART – testicular adrenal rest tumour

are present in 25–40% of LCTs, are not found in TARTs.^{1,3,18} While about 10% of LCTs undergo malignant transformation, no cases of malignancy have been reported in TART patients.^{1,7} In case 2, the initial concerns of testicular carcinoma were dismissed based on tumour marker results and ultrasound findings, which instead indicated TARTs.

TARTs are challenging to detect due to their location in the rete testis, making palpation difficult unless the tumours are > 2 cm.^{1,3,7} Various imaging and laboratory methods are available for detection and assessment. Ultrasound and magnetic resonance imaging are effective modalities, with ultrasound being the preferred choice due to its accessibility, cost-effectiveness, and ability to detect even small adrenal rest remnants.¹

In case 1, no new lesions had developed, but their shift to the mediastinum testis raised concern about testicular dysfunction and infertility. Irregular ultrasound follow-ups delayed early detection. Consistent ultrasound monitoring is crucial for tracking progression and preventing irreversible gonadal damage. While glucocorticoid optimisation is the primary treatment, biopsy should be considered if malignancy is suspected.

TARTs can be categorised into five stages based on ultrasound, according to Claahsen-van der Grinten et al.¹ (Figure 4). Best practice recommends routine ultrasound from age eight to detect early-stage TARTs (Stage 2) before significant testicular damage occurs.¹ Given the patient's history of hyperandrogenaemia, adrenal hyperplasia, and suppressed gonadotropins, earlier imaging could have enabled timely detection. Although imaging cannot identify very early-stage lesions (Stage 1), small hypoechoic lesions become visible in Stage 2, while fibrotic strands appear as hyperechoic reflections in Stage 3 and beyond.¹

Managing TARTs in CAH requires optimised hormonal therapy and, in some cases, surgery.^{2,3} The primary goals are to control tumour growth, preserve testicular function, and prevent fertility complications.¹ Increasing glucocorticoid doses can reduce tumour size in Stages 2 and 3 by suppressing ACTH secretion, improving testicular function.¹

However, this approach is limited by side effects, especially with long-term dexamethasone use, and tumours may regrow when doses are reduced.¹ Despite these limitations, optimising glucocorticoid therapy is crucial for patients with poor hormonal control to achieve tumour regression (Stage 3).¹ Poor adherence to glucocorticoid therapy, as in case 1, can result in persistent hyperandrogenaemia

and disease progression. While glucocorticoid doses can reduce tumour size in Stages 2 and 3, case 2 demonstrates that once fibrotic changes occur (Stage 4), hormonal therapy becomes ineffective, highlighting the need for earlier intervention and alternative strategies, such as the use of long-acting corticosteroids or stricter adherence monitoring.

Evaluating gonadal function involves measuring luteinising hormone (LH), follicle-stimulating hormone (FSH), Inhibin B, and testosterone levels.¹ Gonadal impairment typically becomes evident from Stage 3 onwards.¹ However, in CAH patients, gonadotropin levels may be suppressed due to adrenal androgen excess and subsequent oestrogen conversion, limiting their diagnostic utility.¹⁹ Inhibin B serves as a marker for Sertoli cell function, particularly in prepubertal individuals.²⁰ Semen analysis is recommended for post-pubertal and adult patients.¹ Regular monitoring of ACTH, renin, 17-OHP, and androstenedione is crucial, as TART growth is hormone-regulated.¹ In longstanding cases with infertility, a testicular biopsy may assess residual testicular tissue viability.¹⁸

In case 1, extensive hormonal assessments were conducted, including 17-OHP, dehydroepiandrosterone sulfate (DHEAS), testosterone, and androstenedione, which are valuable for evaluating adrenal androgen excess. However, ACTH and renin monitoring, essential in the literature, were not mentioned. LH and FSH were suppressed due to adrenal androgen excess, limiting their diagnostic utility. Inhibin B, crucial for Sertoli cell function, was not reported; however, it could have provided insights into early gonadal dysfunction. Semen analysis (if applicable) or testicular biopsy was not considered. Given that the patient had persistent hyperandrogenaemia and a history of bone age advancement, testicular function should be closely monitored. In case 2, regular 17-OHP, testosterone, and adrenal androgen measurements were performed; however, LH and FSH were only recorded at age 32, which is much later than ideal. Earlier Inhibin B testing could have better assessed Sertoli cell function.

Angiotensin II may contribute to tumour progression, so adequate mineralocorticoid replacement is necessary to support hormonal balance and potentially limit tumour growth.²¹ In Stage 4, glucocorticoid therapy is less effective, and surgical removal may be considered to prevent further testicular damage.¹ Organ-preserving surgery is recommended due to TARTs' non-malignant nature.¹ However, the guidelines do not specify how often renin, aldosterone, and electrolyte levels should be monitored.¹⁵ Closer mineralocorticoid regulation could help delay TART progression,

especially given the electrolyte imbalances in case 1 and fluctuating adherence in case 2.

Testis-sparing surgery has shown positive outcomes in CAH patients, with good vascularisation and no recurrence, though data on pituitary-gonadal function are lacking. In advanced TART (Stage 5), irreversible gonadal dysfunction may occur, and surgery should focus on symptom management. A testicular biopsy is advised to assess tissue viability before surgery.^{1,13,14} The optimal timing for surgery remains challenging. In case 2, delayed diagnosis and poor treatment adherence led to the formation of mixed, solid and cystic masses with microlithiasis. These advanced lesions present increased surgical complexity and are correlated with reduced preservation of testicular function.

These cases highlight the importance of adhering to treatment, as non-compliance contributed to tumour progression. It is crucial to address psychological and logistical barriers, particularly among adolescents. Comprehensive management requires multidisciplinary care involving endocrinologists, urologists, and mental health professionals. Early intervention involving regular ultrasounds and biopsies is vital to preserve testicular function and fertility. Proactive monitoring can help prevent irreversible damage and the need for surgery.

Future research should focus on key aspects of TART and CAH management. Longitudinal studies should examine the long-term effects of glucocorticoid therapy on testicular function and TART development. Studies are needed to determine optimal screening protocols and therapeutic strategies for managing TARTs and CAH. Personalised approaches considering genetic, hormonal, and lifestyle factors may enhance TART prevention. Research into ACTH's role in TART growth could lead to the development of targeted therapies. Exploring adrenalectomy or testicular-sparing surgery may also offer insights for advanced cases.

Conclusion

TARTs are a significant but manageable complication of CAH. Early detection, consistent glucocorticoid therapy, and regular monitoring are crucial for preserving testicular function and preventing irreversible damage.^{1,3,4} Routine ultrasound screening and hormone assessments should be incorporated into long-term follow-up. Individualised treatment strategies, including early intervention and potential testis-sparing surgery in refractory cases, may improve patient outcomes.^{1,2} Further research into targeted therapies and optimal screening protocols is warranted.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

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