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Case Report

Testicular adrenal rest tumors (TART) secondary to congenital adrenal hyperplasia: A case report emphasizing early detection and management ☆,☆☆

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ABSTRACT

This study highlights the significance of testicular adrenal rest tumors (TARTs) in the context of congenital adrenal hyperplasia (CAH). The case report of an 11-year-old male with bilateral scrotal enlargement underscores the diagnostic challenges and complexities involved. Through thorough clinical, radiological, and hormonal assessments, we elucidate the pathophysiology, prevalence, and potential impact on fertility. Early detection and management of TARTs are crucial for preserving testicular function. Regular scrotal ultrasound screenings are recommended to avert long-term complications in male CAH patients.

Introduction and importance

Testicular adrenal rest tumors (TARTs) also known as testicular tumors of the adrenogenital syndrome are postulated to arise from aberrant adrenal cells which descend with the testes during embryogenesis [1]. Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that is characterized by a deficiency of enzymes involved in the synthesis of glucocorticoids. Glucocorticoid deficiency via a negative feedback mechanism leads to an increase in ACTH (Adrenocorticotropic hormone) secretion resulting in adrenal hyperplasia. It also leads to the overstimulation of aberrant adrenal rests in the testes, resulting in the formation of TARTs [2]. Testicular lesions in the background of CAH were first described by Wilkins et al. [3]. The incidence of TARTs is between 1 and 2 in 20,000 [1,2]. estimated prevalence of TARTs

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in male patients with CAH is 37% [4,5]. Prevalence increases significantly after the onset of puberty [6]. Most TARTs are small and clinically undetectable but can rarely present as a clinically palpable mass [1]. Although TARTs are benign, they can affect testosterone production and lead to infertility due to tubular obstruction [7]. TARTs usually respond to medical therapy [2]. TARTs in the setting of CAH can be diagnosed by the combination of clinical, biochemical, and radiological assessment

Case report

An 11-year-old male had presented to the hospital with a history of bilateral scrotal enlargement noticed in the past 3 months. History of palpitation, restlessness, anger, and dizziness on and off for the past 4-5 years. There was no history of fever or localized pain. On examination, the blood pressure was elevated measuring 150/100 mm Hg on the left and 144/100 mm Hg on the right arm, the rest of the vitals were stable. His body weight was 42.5 kg (75th-90th centile) and his height measured 138 cm (50th centile). Generalized skin hyperpigmentation was present. Systemic examinations were normal. Local examination revealed bilateral scrotal swelling with normal-appearing skin, and bilateral testes were firm on palpation. No localized rise in temperature or tenderness was noted. Tanner staging was done which was stage 3 for genitalia (testis length 3.5 cm, penile length 10 cm) and stage 3 for pubic hair.

The patient presented to our department for ultrasonography of the inguinoscrotal region. Bilateral testis was normal in size (right and left testicular volume – 2.9 mL and 2.8 mL respectively) with multiple well-defined round to oval hetero-echoic nodules with calcific foci within and color Doppler showed increased peripheral and internal vascularity (Figs. 1A, B and 2A, B). On screening abdominal sonography, a large well-defined triangular hypoechoic lesion was noted in the left suprarenal region and a smaller similar lesion in the right suprarenal region without internal vascularity (Figs. 3A and B). Based on these findings, the possibility of testicular malignancy with adrenal metastasis was considered. Contrast-enhanced CT abdomen and pelvis were performed which showed homogeneously enhancing enlarged bilateral adrenal glands (left>right) with maintained shape, suggesting adrenal hyperplasia (Fig. 4A). Bilateral testes appeared hypodense with multiple enhancing nodules within (Fig. 4B and C). Serum tumor markers (alpha-fetoprotein, LDH, and Beta hCG) were negative hence, the diagnosis was reconsidered for the possibility of testicular adrenal rest tumors in an undiagnosed case of congenital adrenal hyperplasia.

X-ray left wrist AP/lateral view was done for estimating the bone age which showed accelerated bone age corresponding to approximately 18 years of age (Fig. 5). The serum potassium concentration was found to be elevated at 5.8 mEq/L (normal range: 3.5-4.5 mEq/L), whereas the sodium level remained within normal limits at 140 mEq/L. There was a significantly heightened level of 17-hydroxyprogesterone at 1800 ng/dL (normal range: <110 ng/dL), accompanied

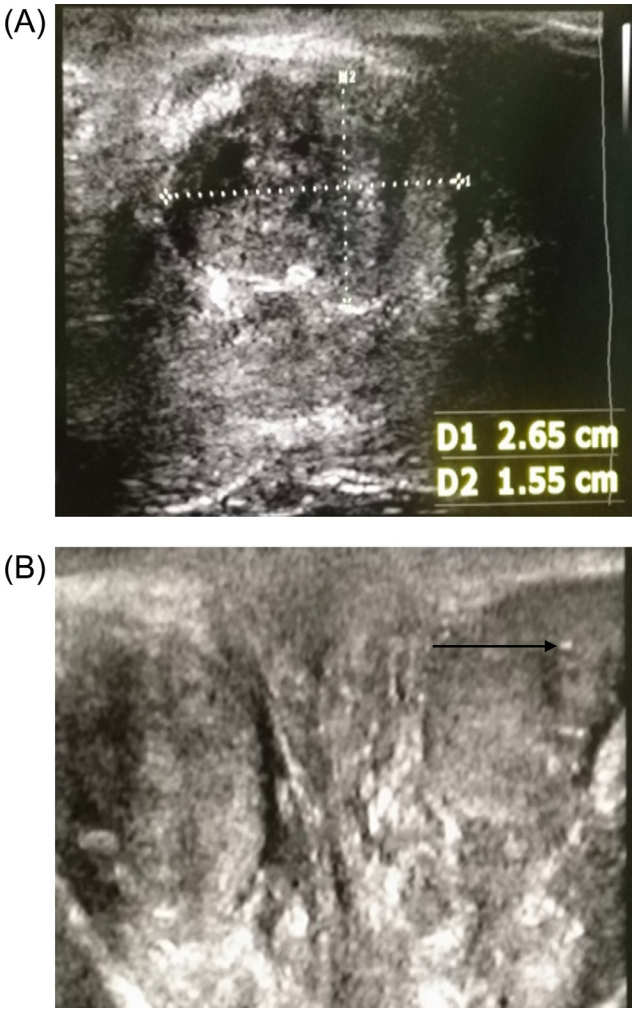

Fig. 1 – (A) Grayscale US of scrotum showing normal-sized right testis with heterogeneous appearance. (B) US image of bilateral testes with multiple nodules containing tiny calcific foci (black arrow).

by normal levels of lactate dehydrogenase (LDH), beta-human chorionic gonadotropin hormone (B-HCG), and alpha-fetoprotein (AFP). Additionally, the serum adrenocorticotropic hormone (ACTH) concentration was elevated, measuring 564 pg/mL (normal range: 7.2-63.3 pg/mL), while cortisol levels were diminished, measuring 5.7 μg/dL (normal range: 7-25 μg/dL). Dehydroepiandrosterone sulfate (DHEA-S) was measured at 5.25 μmol/L (normal range: ≤ 3.726 μmol/L), reflecting an increase. Moreover, androstenedione levels were elevated at 250 ng/dL (normal range: 31-65 ng/dL), and there was a reduced level of Inhibin B, measuring 71.1 pg/mL (normal range: 240-445 pg/mL). Collectively, these findings point towards a diagnosis of congenital adrenal hyperplasia. The patient is currently undergoing treatment with hydrocortisone and is on regular follow-up. The 3-month follow-up revealed clinical improvement with a reduction in testis size and decreased ACTH levels, indicating positive progress.

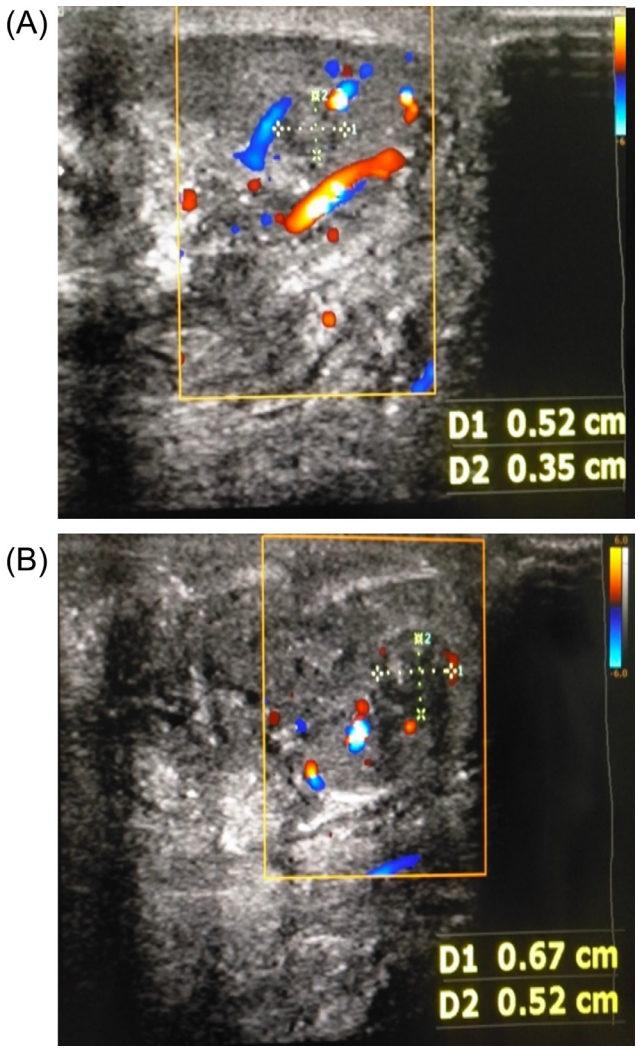

Fig. 2 – (A) Color Doppler US of scrotum showing iso to heteroechoic nodules within right testis with increased vascularity. (B) Color Doppler US of scrotum showing iso to heteroechoic nodules within left testis with increased vascularity.

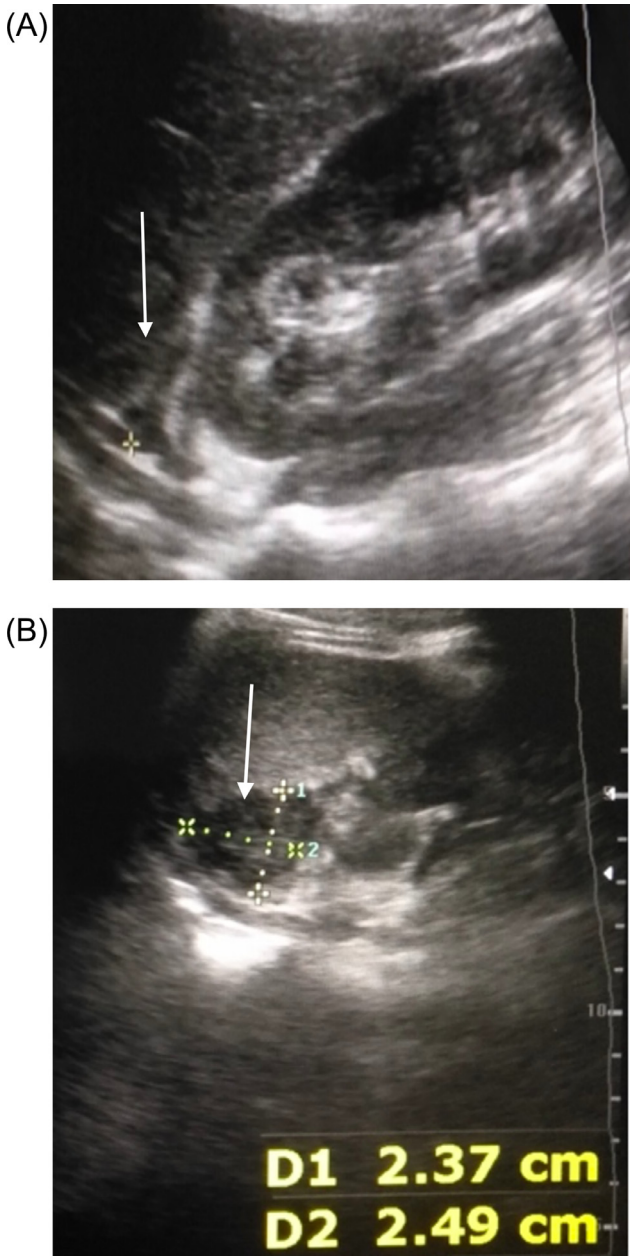

Fig. 3 – (A) Grayscale US of the abdomen showing triangular hypoechoic lesions in right suprarenal regions (white arrow). (B) Grayscale US of the abdomen showing triangular hypoechoic lesions in left suprarenal regions (white arrow).

Clinical discussion

TARTs also known as testicular tumors of the adrenogenital syndrome are postulated to arise from aberrant adrenal cells which descend with the testes during embryogenesis [1]. CAH is an autosomal recessively inherited disease caused by a mutation in the CYP21A2 gene, leading to deficiency in enzymes particularly the 21-hydroxylase enzyme, involved in more than 90% of cases [5].

The deficiency or complete absence of that enzyme leads to inadequate cortisol secretion. The pituitary gland via negative feedback, secretes high levels of ACTH, resulting in hyperplasia of the adrenal gland and increased secretion of adrenal androgens. Chronically high levels of ACTH in patients with CAH are postulated to be the reason behind the development of TART. Additionally, excess androgens cause bone age advancement. Reports have shown the presence of advanced bone age in 66%-100% of patients with TARTs [1,8]. As a result of 21-hydroxylase deficiency, patients with CAH have high serum ACTH, 17-hydroxyprogesterone, and androgens [6,9]. ACTH is thought to be the reason behind the development of testicular tumors, because of the presence of ACTH receptors in testicular tumor tissues. Moreover, ACTH suppression has been shown to maintain or even reduce tumor size [6].

TARTs affect the testes bilaterally in more than 80% of cases. Most children are asymptomatic with no palpable mass. The mass is considered palpable when it reaches ≥2 cm in

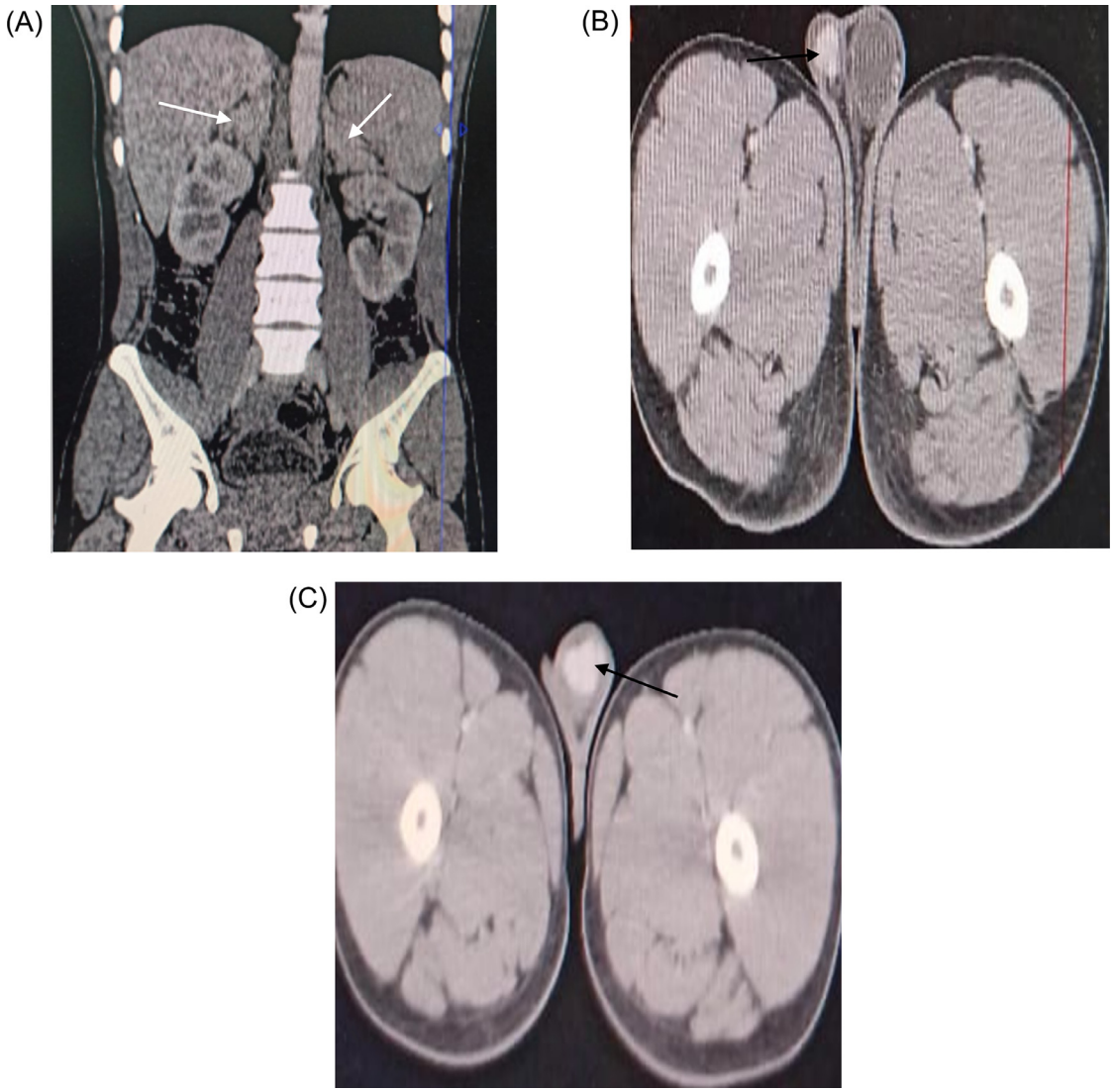

Fig. 4 – (A) Contrast enhanced computed tomography (CECT) image of abdomen in coronal reformatted section showing bilateral adrenal hyperplasia (White arrows). (B) CECT pelvis axial section showing multiple enhancing nodules in the right testis (black arrow). (C) CECT pelvis axial section showing multiple enhancing nodules in left testis (black arrow).

size because of its presence in the rete testes near the mediastinum [10]. Foci of ectopic adrenal rest tissue has been found in 50% of neonates in the retroperitoneum, broad ligament, testes, ovaries, and inguinal canal. These foci usually regress in adulthood. But in patients with CAH, TARTs can occur with prevalence rates of up to 94% [11,12].

TARTs are usually diagnosed in patients with CAH during puberty. This could be due to the rising levels of LH during puberty. Moreover, the presence of LH receptors in testicular tumor tissue also suggests the additional stimulating effects of LH on tumor growth [13].

There are 5 stages of TART: (a) stage 1 (adrenal rest cells within the rete testis; (b) stage 2 (hyperplasia and hypertrophy of the rest cells); (c) stage 3 (rest cells compressing the rete testis); (d) stage 4 (induced fibrosis and lymphatic infiltration of testicular parenchyma) and; (e) stage 5 (irreversible damage of testicular parenchyma) [14].

The clinical severity of CAH correlates with the degree of enzymatic defect. The disease in its severe form results in reduced aldosterone and cortisol production, along with elevated androgens. Androgen excess can cause advanced bone age and short stature while aldosterone deficiency can result in salt wasting that can be severe. In severe cases of CAH, virilization of female fetuses can be seen with male fetuses remaining anatomically normal [15].

Because of the localization of TARTs in rete testis, the tumors may compress the seminiferous tubules leading to obstructive azoospermia. Therefore, it is important to detect and treat the tumors before permanent damage of the testis has occurred [16]. If the excess ACTH is present in the long term and is untreated, the adrenal glands become hyperplastic and nodular and are at an increased risk of tumor formation such as pheochromocytomas and myelolipomas. So, TARTs in the setting of CAH must be treated without any delay [17].

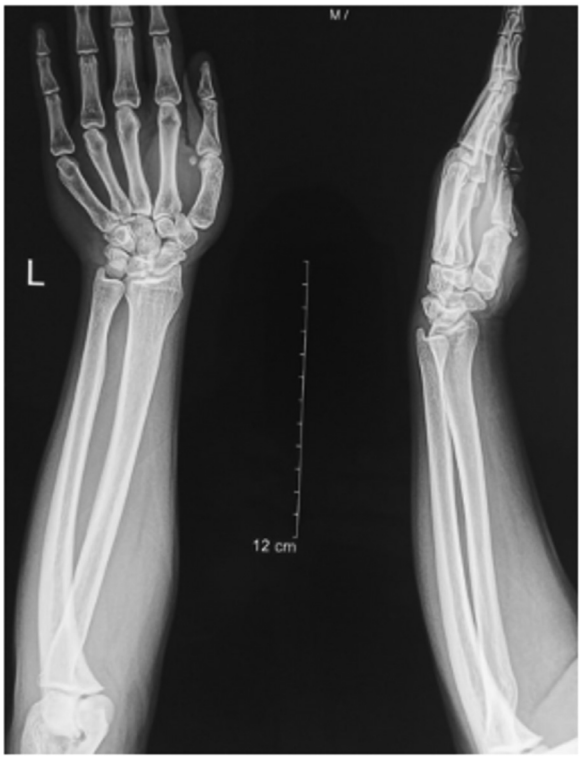

Fig. 5 – X-ray of left wrist AP and a lateral view showing accelerated bone age corresponding to approximately 18 years.

The Ultrasonogram (USG) appears to be the cheapest and the most reliable screening modality for the detection of TARTs in CAH [11]. The USG can also be used to assess treatment response in some patients because improved hormonal control leads to tumor regression [6]. In the US, TARTs present lobular, elongated, predominantly hypoechoic masses with sharp margins, with sizes ranging from 4 to 38 mm. Larger lesions (>2 cm) can have areas of increased echogenicity and therefore may appear heterogeneous. Cystic areas and calcifications are not seen [18]. The sensitivity of the US is similar to that of MRI for the detection of adrenal rest tumors. USG is the modality of choice, given its easy availability and low cost, as compared to MRI. MRI assessment is only preferred only before testis-sparing surgery to know the exact size and extent of the tumor. On MRI, TARTs appear isointense to hyperintense on T1-weighted images and hypointense on T2-weighted images, relative to the normal parenchyma [19]. Contrast-enhanced US is thought to be more advantageous than the US as it provides real-time imaging of vascular flow, even at a microvascular level, and thus tissue perfusion. Disorganized or increased vascularity on contrast-enhanced US is usually considered a feature of malignancy and "washout" is a potential marker of malignancy. Strain elastography provides additional information by adding stiffness as an additional qualitative and quantitative measure of tissue properties. Malignant lesions are usually considered "harder" (less compressible and stiffer) than benign lesions [20].

Treatment of TARTs consists mainly of incremental glucocorticoid dosage adjustments to shrink or maintain tumor size. Prescribing an equivalent dose of dexamethasone has shown some benefits [6]. If glucocorticoid treatment is ineffective, testis-sparing orchidectomy is recommended to save unaffected testicular parenchyma [14].

The major differential diagnoses of TARTs include synchronous malignant testicular tumors. These tumors are rare and occur in only 1%-2% of patients (16]. USG serves as a useful modality to differentiate TARTs from other testicular tumors that are found in a similar age group and patients with precocious puberty (like Leydig cell tumors). Malignant testicular tumors are usually unilateral but can be bilateral in 3% of the patients, whereas TARTs are bilateral in more than 80% of cases. Malignant tumors can occur anywhere in the testis, whereas TARTs usually occur in the specific locations of the testis like the rete testis, and TARTs usually show internal vascularity [10]. TARTs misdiagnosed as Leydig cell tumors can lead to unnecessary orchidectomy. In a series of studies, unnecessary testicular surgery for presumed malignancy has been performed in 6% of the CAH males [21]. Leydig cell hyperplasia could serve as another differential diagnosis of TARTs, but they are usually solitary with a size of less than 5 mm. Lymphomas and Leukemias can present as bilateral testicular masses but, they tend to occur in older patients and are not typically included in the differential diagnosis of testicular masses in young and during puberty. Testicular tumors may be indistinguishable at times, based solely on radiological findings. Therefore, clinical and hormonal features should be taken into consideration. It has been proposed that screening for TARTs in male patients with CAH should start at the age of 8 years [10].

Screening via scrotal US must be performed at least before puberty and regularly during adulthood in male patients with CAH to prevent infertility. It has been recommended that regular screening by scrotal ultrasound should be performed at least every 2 years in early childhood and annually in the peripubertal period [22].

Conclusion

This study underscores the pivotal role of early detection in preserving testicular function and fertility in male CAH patients with TARTs. Thorough clinical and radiological assessments, along with regular scrotal ultrasound screenings, are imperative to mitigate the diagnostic challenges and ensure effective management of this complex condition.

Ethical approval

This case report did not require review by the ethical committee.

Registration of research studies

Not applicable

Provenance and peer review

Not commissioned, externally peer-reviewed

Author contributions

Sasmita Tuladhar: Conceptualization, as mentor and reviewer for this case report and for data interpretation. Shailendra Katwal: Contributed in performing literature review and editing. Hari Om Joshi: Contributed in writing the paper and reviewer for this case. Bhawani Yadav: Contributed in writing the paper and reviewer for this case. Amrit Bhusal: Contributed in writing the paper. Sushmita Bhandari: Contributed in writing the paper. All authors have read and approved the manuscript.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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