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Research Article

Imaging Features of Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia: Our Experience and Literature Review

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Abstract

Aim: Our motive was to evaluate the sonographic and magnetic resonance imaging features of testicular adrenal rest tumors (TARTs) in patients with congenital adrenal hyperplasia, to improve the diagnostic efficiency of these rare testicular lesions.

Methods: We found five male patients of congenital adrenal hyperplasia from our hospital database. All patients were young adolescents (age range = 14 - 16 years), had baseline scrotal ultrasound and MRI and follow up scrotal ultrasound examinations. 4 out of 5 patients had testicular lesions both in the US as well as MRI. All (4) positive cases had bilateral testicular lesions, located near the testicular mediastinum. US and MRI features of these 8 TART lesions in 4 patients were analyzed. We also conducted a literature review of TART in CAH patients.

Results: Key sonographic features of TARTs were: similar heterogeneously hypoechoic bilateral testicular lesions, located near the mediastinum, clear margins, no mass effect and normal testicular vessels coursing through the lesions. Key MRI features were: bilateral testicular lesions with low signal intensity on T2-weighted images, no diffusion restriction and homogenous enhancement (more than the normal testicular parenchyma) on post-contrast T1-weighted images. These features can help radiologists to make an accurate diagnosis of TART.

Conclusion: TARTs are frequently seen in males with congenital adrenal hyperplasia and are often misdiagnosed as malignant primary or other more common benign testicular tumors. Scrotal US and MRI are reliable imaging modalities for diagnosis and follow up of TARTs, with the US, being the initial preferable imaging modality of choice. Screening scrotal ultrasound can be recommended in all males with classic CAH, from the onset of puberty, to avoid future complications, especially infertility. TARTs have a typical imaging appearance that every radiologist must be aware of.

Keywords: *Congenital adrenal hyperplasia; Testicular adrenal rest tumor; Ultrasound; Magnetic resonance imaging*

Abbreviations

CAH: Congenital Adrenal Hyperplasia; TART: Testicular Adrenal Rest Tumor; 17-OHP: 17- Hydroxyprogesterone; ACTH: Adrenocorticotropic Hormone; AII: Angiotensin II; LCT: Leydig Cell Tumor; US: Ultrasound; MRI: Magnetic Resonance Imaging; TR: Repetition time; TE: Echo time; ms: Milliseconds; IV: Intravenous

Introduction

Testicular adrenal rest tumors (TARTs) are rare benign testicular masses that are frequently seen in inefficiently managed patients with congenital adrenal hyperplasia (CAH), regardless of the particular genetic metamorphosis or metabolic management [1-3]. Identifying this affiliation and identifying peculiar sonographic appearances of TARTs is crucial to avert misinterpreting them as mortal cancerous lesions, which can prompt superfluous interventions [1,2]. Early diagnosis of this disease entity is vital, as it only pinpoints poor hormonal management [2]. Furthermore, it can thwart extraneous biopsies and orchiectomies and can preserve virility [2,4].

In males with CAH, TARTs arise from hyperstimulation of abnormal adrenal cells which disembark with the testes during embryogenesis [5]. The majority of the TARTs are small and clinically not palpable [1,5,6]. They are customarily benign; however, due to their imaging appearance of a tumor, sometimes, tissue diagnosis may be necessary to exclude the probability of malignancy [5]. Optimal steroid replacement is the regimen of choice and leads to regression of the lesion in the majority [5].

Methods

Patients

We found 5 male, known cases of congenital adrenal hyperplasia in our hospital database who underwent scrotal US and MRI from April 2018 to March 2019. All patients had a 21-α-hydroxylase deficiency, confirmed with genetic analysis, in the neonatal age group. All patients were young adolescents (age range = 14 - 16 years), at the time of baseline scrotal US and MRI examinations. Four patients had at least two follow-up scrotal ultrasound examinations at 6 months interval. TART was diagnosed by clinical (history and laboratory investigations) and imaging features and no biopsy was done.

US imaging technique

Two ultrasound machines {iU22 (Philips Healthcare, Amsterdam, Netherland) equipped with a linear transducer with a frequency range of 5 - 12 MHz and LOGIQ E9 (GE health care ultrasound, Germany) equipped with a linear transducer with a frequency range of 6 - 15 MHz} were used. All ultrasound examinations were performed by a male sonographer with more than 10 years of experience in ultrasound under the supervision of a consultant radiologist. Both gray-scale and color Doppler ultrasound examinations were performed. Ultrasound images were interpreted by two radiologists with more than 10 years of experience, and the site, size, shape, number, margins, echogenicity, and vascularity of the testicular lesions were carefully recorded in written reports.

MR imaging technique

All scrotal MRI scans were performed on a 3 T scanner (MAGNETOM Verio, Siemens, Germany). The patient was scanned in a supine position with feet first. A scrotal support/folded towel was placed between the patient's thighs to elevate the scrotum to a horizontal plane and the penis was taped to the anterior pelvic wall, out of the area of interest. A circular multipurpose surface coil was centered over the scrotum. T2-weighted axial, sagittal and coronal (TR = 4000 ms, TE = 109 ms, FOV = 200 mm, slice thickness = 3 mm), T1-weighted coronal and axial (TR = 500, TE = 17, FOV = 200, slice thickness = 3), T1-weighted axial with fat suppression (TR = 550, TE = 103), T1-weighted axial vibe (TR = 5.23, TE of 1.86 and 3.10), diffusion-weighted images in axial plane (TR = 4500, TE = 93, with B values of 0, 500 and 1000) and post-contrast T1-weighted images in axial, coronal and sagittal planes (TR = 500, TE = 17) with fat suppression, after intravenous injection of 0.2 ml/kg gadoteric acid (Dotarem, Guerbet, France) were acquired. MR images were interpreted by a consultant radiologist with 10 years of experience in body imaging.

Case presentation

Patient # 1

A 14-year-old boy being treated with hydrocortisone and fludrocortisone had poor hormonal control because of his poor compliance. His adrenocorticotropic hormone (ACTH) levels were 2091, 65.2, 80.0 (reference range = 4.7 - 48.8 pg/ml) in 2016, 2017 and 2020 respectively and his 17-hydroxyprogesterone (17-OHP) levels were 13.1+ nmol/l (normal < 10.9) and 26.78 ng/ml (reference range = 0.00 - 1.10 ng/ml) in 2017 and 2020 respectively. Other laboratory investigations (e.g. aldosterone, renin, etc.) were also poorly controlled. He had an ill-defined heterogeneous hypoechoic mass along with the mediastinum testis bilaterally on the scrotal US; right testicular lesion measured 16 x 16 x 22 mm and left testicular lesion measured 12 x 13 x 18 mm.

Patient # 2

A 14-year-old boy with a neonatal diagnosis of CAH associated with the growth hormone deficiency, delayed bone age and short stature. He had been treated with hydrocortisone, fludrocortisone and growth hormone. CAH had been poorly controlled because of his poor compliance. His adrenocorticotropic hormone (ACTH) levels were 9, 136, 165 (reference range = 4.7 - 48.8 pg/ml) in 2017, 2018 and 2019 respectively. His 17- hydroxyprogesterone (17-OHP) level was 14 ng/l (normal = 0.00 - 1.10 ng/ml) in 2019. He had a well-defined lobulated heterogeneous hypoechoic oval shape mass along with the mediastinum testis bilaterally on the scrotal US; right testicular lesion measured 5 x 8 x 18 mm and left testicular lesion measured 6 x 6 x 19 mm.

Patient # 3

A 16-year-old boy with poor hormonal control being treated with prednisolone. His adrenocorticotropic hormone (ACTH) levels were 1231, < 10, 22.4, 1912 (reference range = 4.7 - 48.8 pg/ml) in 2015, 2016, 2018 and 2019 respectively and his 17-hydroxyprogesterone (17-OHP) levels were 127+, 0.9, 14.76, > 96.96 ng/ml (normal = 0.00 - 2.2 ng/ml) in 2015, 2016, 2018 and 2019 respectively. He had a well-defined lobulated heterogeneous hypoechoic oval shape mass along the mediastinum testis bilaterally on scrotal US; right testicular lesion measured 10 x 12 x 25 mm and left testicular lesion measured 8 x 8 x 25 mm.

Patient # 4

A 15-year-old boy being treated with hydrocortisone and fludrocortisone also had poor hormonal control because of his poor compliance. His adrenocorticotropic hormone (ACTH) levels were 15, 43, 325 pg/ml (reference range = 4.7 - 48.8 pg/ml) in 2017, 2018 and 2019 respectively and his 17-hydroxyprogesterone (17-OHP) levels were 97 and > 50 ng/ml (reference range = 0.00 - 1.10 ng/ml) in 2018 and 2019 respectively. He had a small well-defined rounded heterogeneous hypoechoic lesion measuring 5 x 5 x 6 mm along with the mediastinum testis in either testicle on the scrotal US.

Patient # 5

A 15-year-old boy being treated with hydrocortisone had good hormonal control. His adrenocorticotropic hormone (ACTH) levels were < 10, 26.2, 7.7 (reference range = 4.7 - 48.8 pg/ml) in 2013, 2015 and 2019 respectively and his 17-hydroxyprogesterone (17-OHP) levels were 1.0, 0.5 and 0.5 ng/ml (normal up to 1.1 ng/ml) in 2011, 2013 and 2014 respectively. In 2019, he had a high reading of 17-OHP measuring 12.2 ng/ml (normal up to 2.5 ng/ml). Other laboratory investigations (e.g. aldosterone, renin, etc.) were also within the normal range. He had normal bone age, normal growth and puberty. His scrotal US and MRI were negative.

Results

All patients were 14 - 15 years old at the time of the first scrotal ultrasound examination. Four out of five patients (patients 1 - 4) had poor hormonal control whereas one patient (patient 5) had good hormonal control.

Three patients (patients 1, 3 and 4) had advanced bone age, one had delayed bone age (patient 2) and one had normal bone age (patient 5). None of the patients had any scrotal symptoms or gynecomastia. Scrotal physical examination was unremarkable in all patients. However, due to irregular follow up visits with poor compliance with the treatment reflected by deranged endocrine profile in patients 1 - 4, scrotal ultrasound examination was advised by the treating physician as a baseline investigation to document any testicular adrenal rest tumor. After the ultrasound examination, scrotal MRI was performed on the radiologist's recommendation. Scrotal imaging (US and MRI) was also performed in patient 5 who has good hormonal control.

Four out of five patients (patients 1 - 4 with poor hormonal control) had positive scrotal US as well as MRI examinations. These patients had a lobulated heterogeneous hypoechoic mass along with the mediastinum testis bilaterally on the scrotal US. These lesions had ill-defined margins in patient 1 and well-defined margins in patients 2, 3 and 4. These lesions were oval-shaped in patients 1 - 3 and rounded in patient 4. These testicular lesions had no mass effect, posterior acoustic shadowing, calcifications or significant internal vascularity. The epididymides were unremarkable. Scrotal MRI showed a lobulated lesion with well-defined margins (even in the patient 1 where the lesions had ill-defined margins on ultrasound), along with the mediastinum testis on either side in all patients. All the testicular lesions were isointense on T1-weighted and hypointense on T2- weighted images to the normal testicular parenchyma. These lesions showed no diffusion restriction on diffusion-weighted images when compared with normal testicular parenchyma. These lesions showed homogeneous and more intense enhancement than the normal testicular parenchyma on post-contrast T1- weighted images in patients 1, 3 and 4 (patient 2 refused IV contrast). Based on the history of CAH and abnormal endocrinology profile (e.g. elevated ACTH and 17-OHP levels etc.), these US and MRI findings were compatible with TART and a biopsy was not performed. Patient counseling was done after scrotal imaging and the importance of strict adherence to medical treatment was stressed. However, no significant improvement was seen in the endocrine profile as well as in the size of these testicular lesions on follow up scrotal US examinations of these patients with positive imaging results, during the follow-up visits. The last patient (patient 5, with good hormonal control) had negative scrotal US as well as MRI examinations.

Patient No.	Current Age (years)	Current Height (cm)	Current Weight (kg)	Bone Age	Age at diagnosis of CAH (years)	CAH type	Age at diagnosis of TART (years)	Hormonal control	Palpable testicular lesion
1	16	160	62	Advanced	Neonate	21-α-hydroxylase deficiency	14	Poor	No
2	15	153	82	Delayed	Neonate	21-α-hydroxylase deficiency	14	Poor	No
3	18	162	52.9	Advanced	Neonate	21-α-hydroxylase deficiency	16	Poor	No
4	16	163	92	Advanced	Neonate	21-α-hydroxylase deficiency	15	Poor	No
5	15	165	69.8	Normal	Neonate	21-α-hydroxylase deficiency	No testicular lesion on imaging	Good	No

Table 1: *Characteristics of CAH patients.*

Patient No.	Patient Age (years)	Testicular lesion	Lesion size (mm)	Lesion shape	Lesion Margins	Lesion echogenicity	Vascularity	Calcifications
1	14	R L	16 x 16 x 22 12 x 13 x 18	Oval	Ill-defined	Heterogeneously Hypoechoic	No	No
2	14	R L	5 x 8 x 18 6 x 6 x 19	Oval	Well-defined	Heterogeneously Hypoechoic	No	No
3	16	R L	10 x 12 x 25 8 x 8 x 25	Oval	Well-defined	Heterogeneously Hypoechoic	No	No
4	15	R L	5 x 5 x 6 5 x 5 x 6	Rounded	Well-defined	Heterogeneously Hypoechoic	No	No

Table 2: *Sonographic features of testicular lesions in TART patients.*

Patient No.	T1-weighted	T2-weighted	Lesion morphology	DWI	Post-contrast T1-weighted
1	Iso-intense	Hypointense	Well-defined lobulated	No diffusion restriction	Homogenously enhancing more than the normal testis
2	Iso-intense	Hypointense	Well-defined lobulated	No diffusion restriction	Refused IV contrast
3	Iso-intense	Hypointense	Well-defined lobulated	No diffusion restriction	Homogenously enhancing more than the normal testis
4	Iso-intense	Hypointense	Well-defined lobulated	No diffusion restriction	Homogenously enhancing more than the normal testis

Table 3: *MRI features of testicular lesions in TART patients.*

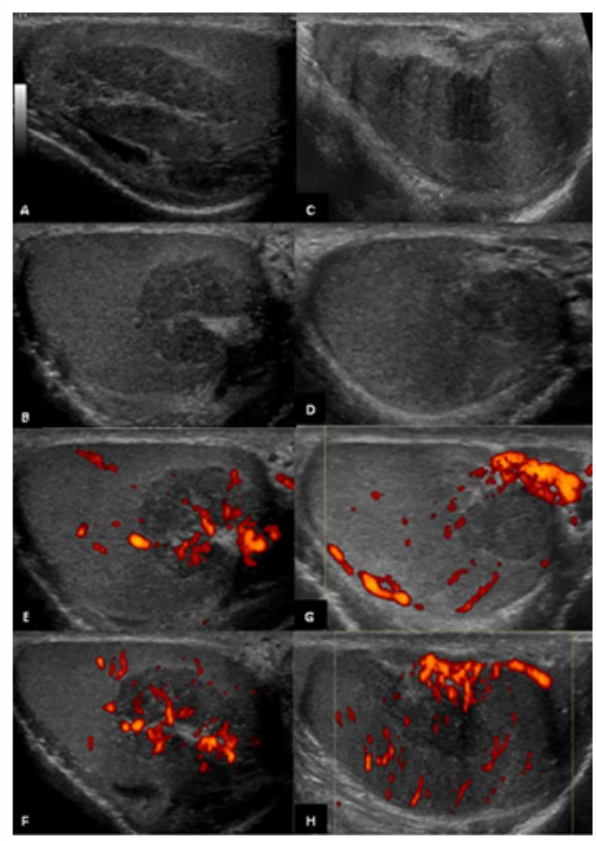

Figure 1: *Testicular adrenal rest tumors (TARTs) in an asymptomatic 16-year-old boy with poorly controlled neonatal CAH (patient# 3). Grey scale US images A, B (longitudinal and transverse images of right testicle), C and D (longitudinal and transverse images of left testicle) show a well-defined lobulated heterogeneous hypoechoic oval shape mass adjacent to the mediastinum testis bilaterally. Color Doppler US images of the right (E, F) and left (G, H) testicles show testicular vessels coursing undisturbed through these masses, without any displacement or change in caliber.*

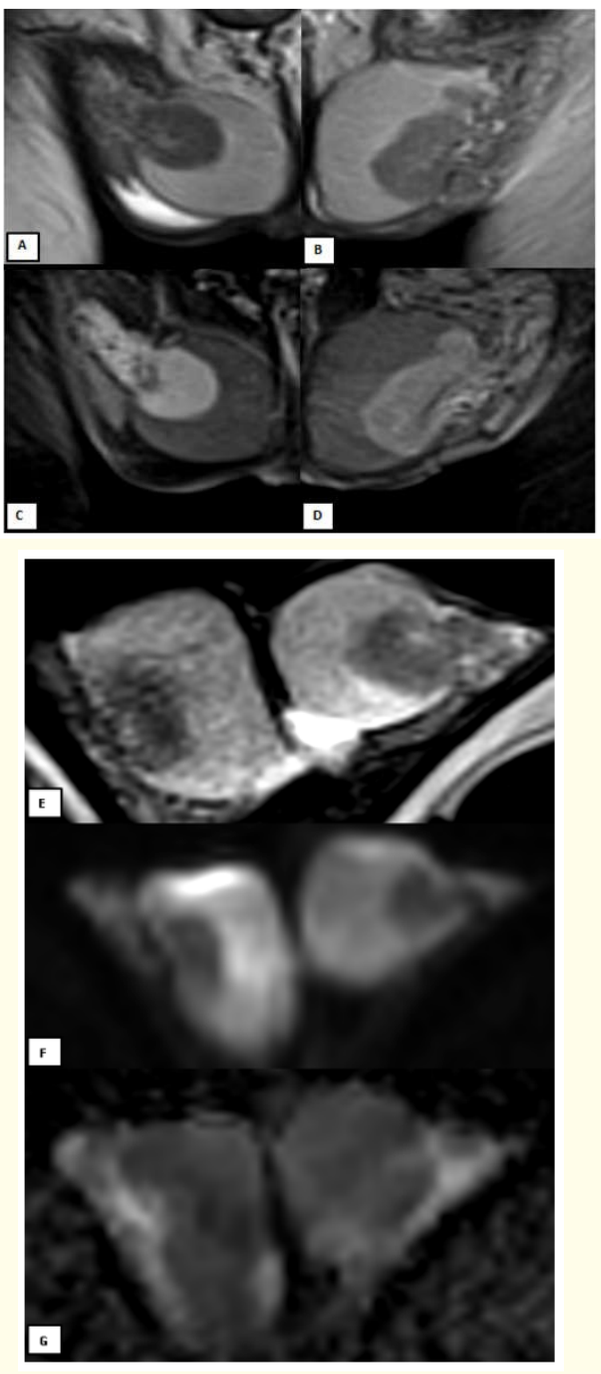

Figure 2: *MRI of testicular adrenal rest tumors (TARTs) in the same patient as in figure 1 (patient# 3). Sagittal T2-weighted images of right (A) and left (B) testicles show an intra-testicular mass that is hypointense to the normal testicular tissue. Sagittal post-contrast T1-weighted images of right (C) and left (D) testicles reveal marked enhancement in these masses that is greater than that of normal parenchyma. These lesions were isointense to the normal testicular parenchyma on T1-weighted images (not shown). Axial T2-weighted image (E) shows an eccentric mass adjacent to the mediastinum testis, that is hypo intense to the normal testicular tissue. These lesions show no restriction on axial b1000 diffusion- weighted image (F) with corresponding ADC map (G). Note diffusion restriction in the normal surrounding testicular parenchyma.*

Discussion

Congenital adrenal hyperplasia (CAH) is an inborn autosomal recessive (AR) derangement of adrenal glucocorticoid synthesis [1-3,7-11]. Mutation in the CYP21A2 gene that results in the deficiency of 21-α- hydroxylase (CYP21) is the cause in more than 90% cases, while the remaining cases are due to deficiency of 11-hydroxylase [1,3,4,7-10,12,13]. The CYP21 enzyme translates progesterone into 11-deoxycorticosterone and 17-hydroxyprogesterone (17-OHP) into 11-deoxycortisol, the forerunners of aldosterone and cortisol respectively [1,8]. Individuals with deficient CYP21 enzymes have decreased levels of glucocorticoids and mineralocorticoids, which causes a decrease in negative pituitary feedback and leads to an increase in adrenocorticotropic (ACTH) production from the pituitary gland. Elevated ACTH level causes adrenal gland hyperplasia, hyperstimulation of ectopic adrenal tissue within the testicles and increased production of adrenal androgens [1-3,7,8,10]. Flawed production of glucocorticoid (cortisol) and mineralocorticoid (aldosterone) may lead to an Addisonian crisis, salt depletion and dehydration in the newborn [1,7,8,14]. Excessive production of adrenal androgens often results in the ambiguous external genitalia in female newborns at birth [1,7,8,14].

The prevalence of congenital adrenal hyperplasia discernible in children is approximately 1 in 10,000 - 20,000 births [1,3,8,11,14,15].

Currently, the most serious forms of CAH can be recognized earlier by neonatal screening programs or even by prenatal diagnosis in case of positive family history, which can aid in avoiding deadly incidents [7]. CAH patients are prone to develop some complications and some of these complications might be detected in childhood [7].

Evolution of benign intratesticular tumors, simulating adrenal tissue, known as "testicular adrenal rest tumors (TARTs)" in endocrinology and radiology literature [1,2,4,7,10] and testicular tumors of the adrenogenital syndrome (TTAGS) in the pathology literature, are amongst the most predominant and common complications of CAH [1,5,6]. TARTs are rare testicular tumors, seen predominantly in male patients with CAH [4,7,10]. TARTs can also be rarely seen in cases with Cushing syndrome [8,16,17].

TART (testicular lesion in the context of CAH) was initially reported by Wilkins., *et al*. in 1940 [1-3,5,7,9]. It has been speculated that testicular adrenal rest tumors (TARTs) originate from ectopic adrenal tissue that nestles within the testicles during embryonic development [1,2,4,5,7,8,10]. Up to 50% of healthy newborns, can have ectopic adrenal rest cells in the retroperitoneum, inguinal region, broad ligament, ovaries, and testes [1-3,5]. In normal people, during development, this ectopic adrenal tissue undergoes atrophy and persists in < 1% of individuals [1,3,5]. However, TARTs are relatively common, in male patients with CAH, with a widely variable described prevalence ranging from 0 - 94% [1,3,4,7-9,18-25]. According to some studies, TARTs may be seen in children, and have a rising preponderance around puberty [4,10,26-28]. Kim., *et al*. advocated that the incidence of TART is high in young men with CAH, but low in infants or elderly patients [8,29].

ACTH levels have a major role in the pathogenesis [4,5,8,10,21]. Mazzilli., *et al*. have shown ACTH level as a crucial prognosticator of TART ($p < 0.05$), increased ACTH levels in all cases with TART and normal levels in cases without TART and the substantial correlation between the decline of ACTH concentrations and regression of TART diameters ($p < 0.5$) [8]. Modification of the glucocorticoid treatment with a significant drop in plasma ACTH reading equated with a decrease or complete resolution of the TARTs in more than 75% of patients [8]. They also found significantly higher ACTH and 17-OHP concentrations in patients with TARTs than in patients without TARTs ($p < 0.01$) [8]. Ma., *et al*. also reported a potential relationship between ACTH value and tumor size ($p = 0.066$) [10].

Etiology and physiology of TART

The exact etiology and physiology of these tumors are still not completely known [7]. The most likely cause for the development of TART is the presence of aberrant adrenal tissue within the testicles. This hypothesis can explain the frequently recognized dispar-

ity between the development of a tumor and hormonal regulation. It is presumed that TART will no way enroot in those CAH patients who do not have preexisting intratesticular ectopic adrenal rest cells [7]. A few studies have shown 21-deoxycorticosterone (21DB) and 21-deoxycortisol (21DF) {adrenal specific steroids}, in gonadal vein blood samples, which illustrates the habitation of adrenal- like tissue within the testicles of these CAH subjects with 21-hydroxylase insufficiency [6,7].

Suppression of ACTH level (by high doses of corticosteroids) can cutback TART size and high values of ACTH (patients with poorly managed CAH or patients with Nelson's syndrome) can increase tumor size; these findings are suggestive of the existence of ACTH receptors on these tumor cells [7,9,10,30,31]. There are also reports of receptors of adrenal specific enzymes CYP11B1 and CYP11B2 and angiotensin II (AII) in the TARTs. Hence, it might be contemplated that in CAH patients, the proliferation of TART may not only be aroused by elevated ACTH levels but also by high AII levels (as seen in salt-losing CAH patients with indigent hormonal management) [7]. However, it is noticed that suppression of ACTH level with combative steroid treatment does not always curtail tumor size and that these tumors have also been seen in patients with well-controlled CAH, with normal or low plasma ACTH levels; these observations are evocative of some other anonymous elements which regulate tumor growth [7,10,30,31]. It is noticed that mildly or occasionally high ACTH (and AII) levels may boost the growth of these intratesticular rest cells which can explain the existence of TART in early age, even in the judiciously treated patients and this process can even be worsened in patients with indigent hormonal regulation with markedly increased ACTH concentrations. Besides, these rest cells may already be stimulated by high ACTH levels in utero [3,7]. LH receptors are also seen in TART and LH elevation at the time of puberty may also furthermore expedite the tumor growth which may illustrate the higher preponderance of these tumors in pubertal and post-pubertal CAH patients even in patients with excellent hormonal management [7]. In summary, tumor growth depends on both the levels of and the span of exposure to such growth encouraging determinants [7].

Life-long effects of TART

TARTs are benign tumors, have no malignant predilection and thus do not need surgical excision at an early stage. Nevertheless, due to their central position next to the mediastinum testis, TARTs can compress the seminiferous tubules and cause obstructive azoospermia, irrevocable demolition of the neighboring testicular tissue and infertility [3,4,7,8,10,27,30,32]. High ACTH levels also indirectly impair spermatogenesis [8,18]. TARTs also produce steroids which may have a paracrine impact on the testicular parenchyma [7].

Recommended staging of TART

Based on cytology of TART, neighboring testicular tissue and the clinical features Claahsen-van der Grinten HL., *et al*. suggested that the evolution and progression of TART may be categorized into five distinct stages (Table 4 and figure 3) [7,24].

	Histological description	Reversibility	Treatment option
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)	+++	Optimizing glucocorticoids
Stage 3	Further growth of the adrenal rest cells with (reversible) compression of the rete testis	++	Optimizing glucocorticoids Surgery?
Stage 4	Induction of fibrosis and focal lymphocytic infiltrates	-/+	Surgery?
Stage 5	Irreversible damage of the testicular parenchyma. Parts of the tumor are replaced by adipose tissue.	-	-

Table 4: *Recommended staging, prognosis and management options of TARTs [7].*

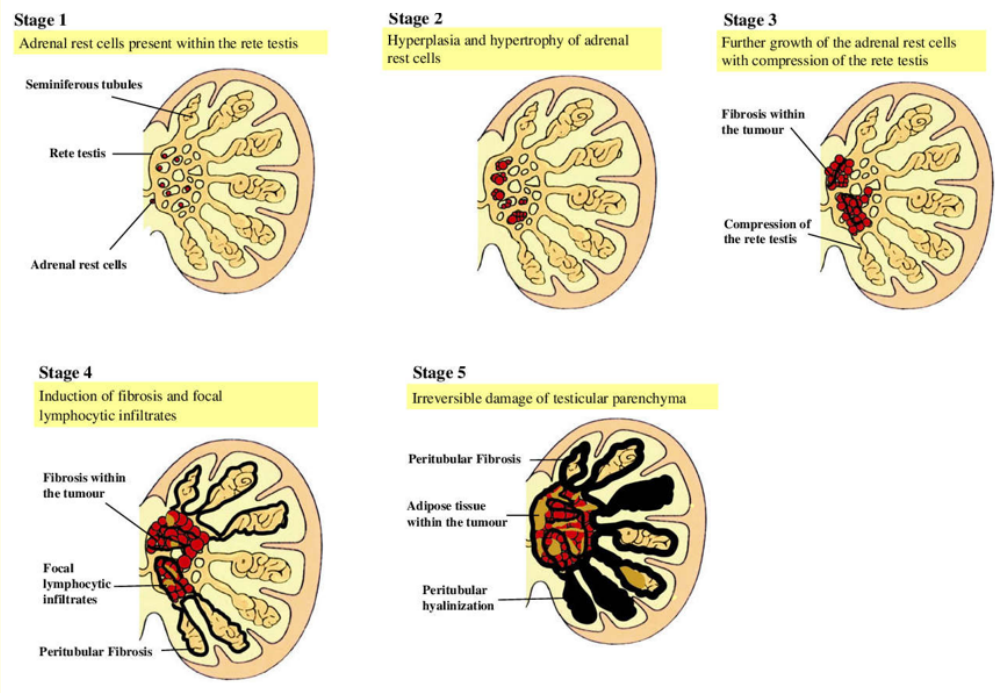

Figure 3: *Diagrammatic illustration of the staging of TART [24].*

- **Stage 1:** Stage 1 can be described by the ubiety of aberrant adrenal tissue within the testis, which probably revert in utero or the early years of life in healthy objects. It is not appreciable on the ultrasound examination.
- **Stage 2:** In cases of CAH with high levels of growth-stimulating elements like ACTH (and probably AII), the aberrant adrenal tissue may mushroom and is seen as a small hypoechoic lesion on ultrasound examination.
- **Stage 3:** The adrenal rest cells show further growth and may squash the rete testis and obstruct the seminiferous tubules, which is still reversible with optimizing glucocorticoids. Pubertal or post-pubertal CAH patients may have oligo- or azoospermia and signs of gonadal dysfunction.
- **Stage 4:** Further expansion of the adrenal rest tissue with continuous/gradual hindrance of the rete testis may result in the initiation of fibrosis in the tumor. Multiple small focal lesions within the testis will amalgamate into a solitary-lobulated structure which is separable from the remaining testicle by fibrous bands. At this stage, high dose steroids are likely not sufficient in reducing tumor size because of fibrosis.
- **Stage 5:** Long-standing obstruction will finally result in permanent annihilation of the adjacent testicular tissue.

Clinical features and imaging

TARTs are benign tumors and are bilateral in > 80% of the cases [1,2,5-7,9]. Due to their juxtaposition to the rete testis, TARTs < 2 cm are commonly not clinically palpable [1,2,5-7,9]. Thus, they can be readily overlooked if the patient is not evaluated with diagnostic imaging such as magnetic resonance imaging (MRI) or ultrasound [7]. TART invariably accompanies with clinical features of CAH, such as increased weight, decreased height, genital ambiguity, excessive body hair, increased skin pigmentation, early hypertension, and adrenal deficiency symptoms (vomiting, dehydration) [3,8,10,11,14,25,30,33]. Severe CAH can be usually diagnosed earlier by neonatal screening programs; however, milder forms of the CAH may be diagnosed in late childhood to early adulthood [1].

Ultrasound (US) and magnetic resonance imaging (MRI) are comparable modalities for recognition and follow- up of the TARTs; however, ultrasound is quick, cheap and easily available, which is preferred as the initial imaging modality over MRI [1,2,7,10]. Because of its low prevalence and limited radiological literature of sonographic features of TART; most radiologists misdiagnose it as an aggressive malignancy, which may result in superfluous testicular biopsies or orchiectomies [10,34].

The true incidence of sonographically diagnosed TART is not known, because most boys with CAH do not undergo screening scrotal ultrasound routinely [1]. Different pediatric studies reported a prevalence ranging from 18.3% to 29% [1,2,4,7,27,30]. The sonographic appearance depends on the stage of TART. Stage 1 TART cannot be detected with any imaging technique. Stage 2 TARTs are seen as small well-delineated hypoechoic lesions neighboring the rete testis and are usually bilateral [1,2,7-9]. Fibrosis seen as hyperechoic reflections can be found in lesions greater than stage 3 [7]. The size of these tumors is highly variable; according to Delfino., *et al*. these tumors vary in size from 4 - 38 mm [1,2,21].

A great variation is seen in the vascularity of TART on color Doppler ultrasound examination [1,2]. Interestingly, different researches had different opinions; Wang., *et al*. [4] reported 76.7% (23/30) lesions with increased vascularity whereas Delfino., *et al*. [21] reported 72% (8/11) lesions with no internal vascularity. No mass effect or change in caliber in the vessels coursing through the TART lesions is another additional remarkable feature which is not described for other testicular lesions and can be used in discriminating TARTs from other testicular tumors [4].

The majority of TARTs are bilateral whereas the majority of malignant tumors are unilateral. It is an excellent differentiating imaging feature; however, it should be acknowledged that unilateral testicular lesions cannot completely exclude TART [10]. Similarly, clear boundary/sharp margin is a conspicuous but nonspecific feature of TART, as other testicular tumors (teratoma, Leydig cell tumor, and seminoma) can also have this sonographic feature [10].

There is no routine screening program for the detection of TARTs in patients with CAH [7]. Different investigators have recommended screening scrotal ultrasound in childhood; however, there is no consensus about the age of screening in children due to limited knowledge [2-4,7,10,27,35]. Claahsen-van der Grinten., *et al*. [7] suggested starting an annual screening scrotal ultrasound at eight years whereas Zehra Aycan., *et al*. recommended biennial screening scrotal ultrasound in early childhood and annual scan around the puberty [2,27,35].

Ultrasound is also an ideal follow up imaging modality in CAH patients with TARTs and can aid in preventing different gonadal complications, particularly infertility [10,27,35].

The significance of MRI in the interpretation of TARTs has not been meticulously endorsed [1]. According to one comparative study sensitivity of ultrasound is equivalent to MRI in the recognition of TARTs, and thus is the front line imaging modality [1]. However, according to some authors outlines of these tumors are better delineated at MRI. Specifically, MRI may be preferable in discriminating several small, distinct tumors from a single, bulkier multilobular tumor. Hence, in situations when definite information about the magnitude of the tumor is mandatory (e.g. before testis saving operation), MRI is usually favored over the US [1,2]. TARTs are generally of the same

signal intensity on T1 and uniformly of low signal intensity on T2-weighted images, relative to the neighboring healthy testicular parenchyma [1,8,17]. TARTs show more intense homogeneous enhancement than the testicular parenchyma on post-contrast MRI [8].

Traditional MRI had a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of 100%, 80%, 86.5%, 100% and 90% respectively in distinguishing malignant and benign testicular tumors [36]. The characterization of the tumors is further augmented when traditional MR images are reported in combination with diffusion weighting (DW) imaging. Normal testis shows restriction (high signal intensity) on diffusion weighting (DW) imaging [36]. In comparison to normal tissue and benign lesions, malignant tumors have high signal intensity on high-b-value DW imaging (b800 or b1000) with corresponding low ADC values [36]. Benign testicular pathologies show no diffusion restriction [36]. Algebally AM., *et al*. reported low ADC values for malignant testicular lesions when compared with the normal testis and benign lesions (P, 0.000) and no gross disparity in the ADC value between benign testicular pathologies and normal testicular parenchyma (P, 0.004) [36]. Pathologies with ADC value ≤ 0.99 are likely malignant; this value had a sensitivity, specificity, positive predictive value and negative predictive value of 93.3%, 90%, 87.5% and 94.7% respectively [36]. Radionuclide scintigraphy is used in the assessment of primary adrenal tumors; however, its contribution to the appraisal of TARTs is not established until now [1].

In Ma., *et al*. [10] study 87.5% (7 of 8) patients showed bilateral testicular lesions. All lesions had well-defined outlines, 66.7% (10/15) tumors were uniformly hypoechoic, 4/15 (26.7%) were variably iso-hypoechoic, 1/15 (6.7%) were uniformly isoechoic and 10/15 (66.7%) tumors showed increased vascularity [10]. A follow-up of 5 patients showed a change in testicular lesions after glucocorticoid therapy. Strikingly, the same features (margins, echogenicity and vascularity) were acknowledged in either testicular lesion in all patients with bilateral testicular lesions [10]. This feature had also been confirmed by Wang., *et al*. [4], Defino., *et al*. [21] and other studies [2].

Ma., *et al*. [10] also reviewed the literature since 1990, including 23 articles with 123 cases having a sum of 223 TARTs. They found bilateral tumors in 100/123 (81%) patients and 95% of these tumors were adjacent to the mediastinum. 80/103 (78%) patients had lesions with a clear boundary; decreased echogenicity was observed in 164 (74%) tumors, heterogeneous echogenicity in 41 (18%), and increased echogenicity in 18 (8%). 75/106 (71%) of the tumors were round/oval and 29/106 (27%) were lobular. A great variation was seen in the vascularity; 39/152 (26%) tumors had no vascularity, 25/152 (16%) had minimum vascularity, 31/152 (20%) had modest vascularity, and 52/152 (34%) had considerable vascularity. 44 patients with 79 lesions underwent follow-up scrotal ultrasound examination; 29 (37%) remained stable, 29 (37%) regressed and 21 (27%) disappeared [10]. In the study of Mazzilli., *et al*. also more than 80% of the lesions were bilateral and none of the patients had gynecomastia [8].

Laboratory investigations

Serum ACTH and 17-OHP concentrations are used to access hormonal control. Because of short half-life and highly variable secretion, ACTH level is not trustworthy whereas 17-OHP, indirectly reflecting ACTH effects, has a longer half-life and is more reliable [9].

Blood LH (luteinizing hormone), FSH (follicle-stimulating hormone), testosterone and inhibin B levels are valuable in the assessment of testicular activity, as some form of testicular insufficiency is expected in patients with stage 3 onwards. Please note that increased adrenal androgens may suppress gonadotropins (LH and FSH) and hence LH and FSH are useless in the assessment of testicular activity. Patients with CAH usually have normal or only mildly low testosterone concentrations due to high adrenal androgens. In pre-pubertal children, Inhibin B is an excellent investigation for evaluation of gonadal function. Serum 17-OHP, androstenedione and renin levels can also be used in monitoring tumor growth [7].

A semen analysis can be done in adult and (post) pubertal patients. Testicular biopsy is valuable in evaluating the condition of remain-

ing gonadal tissue in longstanding (stage 4 or 5) tumors in CAH patients with infertility. Testicular biopsy is also robustly recommended before any surgical intervention [7].

As TARTs develop only in those patients who harbor aberrant adrenal cells in their testes, which at present can only be diagnosed after their considerable growth; it is crucial to identify such patients at early stages. We expect advanced state-of-the-art diagnostic modalities in the future, which may not only help in early detection of these adrenal rests which can later be followed and managed more comprehensively, but also helps in finding the patients without these adrenal rests where unnecessary imaging, surveillance and invasive management plans could have refrained [7].

Differential diagnosis

As described that TARTs are commonly bilateral; diseases that affect bilateral testes must be contemplated in the differential diagnosis [1].

TARTs are frequently confused with Leydig cell tumors (LCTs). Clear distinction between malignant LCT and TART is challenging on histopathology; however, there are some clinical features which can help in differentiating these tumors: majority (> 80%) of TARTs are bilateral while only 3% of LCTs are bilateral, Reinke crystals, seen in 25 - 40% of LCTs, are missing in TART, and malignant degeneration which is not a feature of TART is reported in 10% of LCTs (only in > 50 years old patients) [1,2,5-8,10]. Synaptophysin and CD56 strongly positive in TART (evocative of neuroendocrine origin), are hardly reported in LCTs [1,5,6]. Androgen receptor-positive in 85% of patients with LCT, is negative in TART [5,6]. Inhibin-alpha is positive in both LCTs as well as TART [1]. Gynecomastia is seen in 30% of patients with LCTs [6,8].

Lymphoma: This occurs in an older population (the commonest testicular neoplasm in men > 60 years) and has a poor prognosis. Lymphoma is the commonest bilateral testicular tumor (bilateral in up to 38% cases). The epididymis and spermatic cord are commonly involved. Testicular lymphoma usually appears as a discrete hypoechoic lesion. The patient's age at presentation, symptoms, and medical history, as well as the multiplicity and bilaterality of the lesions, are all important factors in making the appropriate diagnosis [1,2,17].

Primary leukemia of the testis is rare. However, the testis is a common site of leukemia recurrence in children, with 80% of patients being in bone marrow remission. The sonographic appearance of testicular leukemia is quite variable and these tumors may be unilateral or bilateral, diffuse or focal, hypoechoic or hyperechoic [2,17].

Sarcoidosis is a chronic non-caseating granulomatous multisystem disease that rarely affects the genital tract. In autopsy series, 5% of cases will have genital involvement. It more commonly affects the epididymis but can, in some cases, also involve the testis. Testicular lesions can be solitary, but they are more typically multiple, small, bilateral hypoechoic masses. Testicular sarcoidosis is more prevalent in African-Americans than in other racial groups [1,17].

Epidermoid cyst/keratocyst (the commonest benign testicular tumor) is usually a well-defined, decreased echogenicity non-vascular testicular lesion that may be mixed with TART. It displays a classical lamellated "onion skin" with altering increased and decreased echogenicity rings on ultrasound, which help in discriminating it from TART [1].

Unfortunately, radiological features of TARTs are not specific, and often overlap with malignant testicular tumors like sex cord tumors or primary germ cell tumors; however, these primary testicular malignancies are robustly fewer in number and affect one testis [1].

Gonadal vein sampling showing increased cortisol levels as compared with peripheral blood levels can aid in establishing the correct diagnosis of TART if there is any ambiguity on imaging [1,17].

Treatment

The stability or change in size and morphology of TART depends on how CAH is managed [2,9]. Previous studies have shown that TART may regress when hormonal control is adequate and alternatively may progress when hormonal control is inadequate or when the patient's compliance is poor [1-3,9,27]. The first-line treatment of TART is intensifying glucocorticoid therapy [1,3,7,8,10,37-39].

Optimizing glucocorticoids may result in regression of the tumor size by inhibition of ACTH secretion and may improve gonadal activity in the 2nd and 3rd stages [1,7,9]. Due to some literature reports of failure of reinforced glucocorticoid therapy, only temporary improvement in tumor growth and severe unwanted complications of long-term steroid use (obesity, diabetes, insulin resistance, and osteoporosis), some patients may refuse this management option [3,7,8,14,15,37,40-42]. Nevertheless, intensifying glucocorticoid treatment is essential, particularly in patients with inadequate hormonal discipline to determine tumor growth reversibility (Stage 3). As AII may also arouse the tumor growth, mineralocorticoid therapy also has to be enhanced [7].

Being benign, TART can be treated with testis-sparing surgery [3,7,43]. In stage 4 TART and untreated TARTs, surgical excision of the TART may prohibit further testicular loss [1,7]. However, persisting stage 5 TART with gonadal failure, may not benefit from surgery and gonadal biopsies are recommended to appraise the nature of the neighboring gonadal tissue before any surgical intervention [7]. In stage 5 TART, chronic testicular pain/discomfort is the only implication for surgery [1,7].

In children, the role of testicular surgery for TART is not yet endorsed and further studies are required in this age group to interrogate its benefits [7].

Due to the lack of perfection of pharmaceutical and operative management of TART, patients must be aware of the adverse consequences of TART on potency and sperm banking should be considered as early as possible in adult patients [3,7,38]. Due to the presence of adrenal rest cells during embryogenesis, it is obvious that TART is unavoidable [7].

Our results {clinical features (age of the patients, high prevalence of TART in poor hormonal control) and imaging features of both US and MRI} are in accordance with the previous studies, which is the main strength of the study. However, at the same time, our study has certain limitations. Small sample size, which is likely due to the low incidence of CAH, is the main limitation. Other limitations are lack of evaluation of sensitivity and specificity of each characteristic imaging feature (of both US & MRI), the exact relationship between TART size and poor hormonal control, short follow-up duration and lack of patients with scrotal MRI for other testicular pathologies, particularly of malignant nature. In the future, therefore, further, more thorough and well-designed case-control studies with a larger sample size are necessary to address these limitations.

Conclusion

Testicular adrenal rest tumors (TARTs) are rare benign testicular tumors, usually seen in men with congenital adrenal hyperplasia (CAH). TARTs frequently appear as bilateral, multiple, hypoechoic testicular masses on scrotal ultrasound, which is the first-line radiological technique in diagnosis and surveillance of these tumors. MRI is beneficial in the precise mapping of the disease extent especially before the testis sparing surgery.

TARTs have no malignant potential but long-lasting TARTs can cause permanent damage to the testicular parenchyma and subsequent

infertility. TARTs are probably reversible, as shown by the regression in size after modification of steroid therapy and suppression of plasma ACTH levels. Optimizing glucocorticoid treatment is the first-line treatment option of TART. Testicular biopsies are recommended to appraise the condition of the adjacent testicular parenchyma before testis-sparing surgery.

Radiologists must be familiar with this benevolent disease process in the context of CAH to avoid misdiagnosis and futile biopsies and radical orchiectomies.

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Declaration of Interest

The authors have no conflict of interest to disclose.

Availability of Data

The data/material of this study is available on request to the corresponding author.

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Volume 3 Issue 7 July 2020