

Proposed TART-RADS Classification for Testicular Ultrasound: Our Experience and Literature Review

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Abstract

Background: Testicular adrenal rest tumors (TARTs) are an important complication in patients with Congenital Adrenal Hyperplasia (CAH). Ultrasonography is the diagnostic modality of choice. In this study we examined the possibility of sonographic classification of TARTs in the Reporting and Data Systems (RADS) imaging format.

Methods: 35 male patients with the diagnosis of congenital adrenal hyperplasia due to 21 hydroxylase deficiency were evaluated.

Results: 19 patients had one or more sonographic findings of TARTs. No significant relation was found between 17 Hydroxyprogesterone (17 OH p), ACTH and androstenedione levels in patients with and without TARTs. Five sonographic patterns for testicular lesions were found. The five-stage classification of sonographic findings of TARTs is matched with histological classifications.

Conclusion: This classification system will allow clinicians to perform more accurate approaches. In general, TARTs should be considered in male patients with CAH. Sonography is a good imaging modality for the diagnosis of TARTs. TART-RADS imaging of lesions will allow clinicians to develop more accurate and appropriate approaches.

Key Words: Adrenal Rest Tumor, TART-RADS, Ultrasound Classification.

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1- INTRODUCTION

Testicular adrenal rest tumors (TARTs) are a delayed complication of male patients with congenital adrenal hyperplasia (CAH) (1). They are the growth of the ectopic adrenal remnant tissue in the testicles from the embryonic period, which has become hyperplastic within the testicular parenchyma. These benign tumors enlarge with the advance of age and because of their proximity to rete testis, the compression causes tubular obstruction and may result in oligo/azoospermia in adulthood. Furthermore, large TARTs can also destroy normal testicular parenchyma and affect spermatogenesis and testosterone production (1- 3). Nevertheless, huge testicles may interfere with walking and normal lifestyle.

Therefore, early detection and appropriate treatment of TARTs is mandatory for the prevention of gonadal failure, infertility (1), and the resultant lifelong complications. Inadequate control of CAH is considered as an underlying reason for TART growth. So, their growth can be regressed by intensification of the therapy (4).

Based on the histology of TARTs, parenchyma of testicle, and clinical features, Claahsen-van der Grinten H L *et al.* have proposed that the development and growth of TARTs can be divided into five different stages (5). This classification is being used for changing the severity of disease control and assessing the response to treatment and fertility. With this background in mind, the present study was carried out to examine the possibility of sonographic classification of TARTs in the Reporting and Data Systems (RADS) imaging format and evaluation of proposed TART categories in comparison to the laboratory findings of TARTs.

2- MATERIALS AND METHODS:

This present cross-sectional study was ratified in the Outpatient Radiology and Endocrinology Clinic of Akbar Children's Hospital, Mashhad, Iran, within 2017 to 2020.

The participants of the study included 35 male patients ranging between 8 months to 22 years of age diagnosed with the classic type of 21-hydroxylase deficiency (21-OHD), who had referred to the Radiology Department. The diagnosis of classic 21-OHD was verified by biochemical and/or genetic testing. Furthermore, the cases with incomplete medical records were excluded from the study. The subjects underwent a testicular ultrasound. Testicular ultrasound was performed by an expert pediatric radiologist focusing on sonographic signs of TARTs using Esaote Class C with 7.5-16 MHz multi-frequency probes. Several images of testicles in sagittal and transverse views for each patient were saved for further analysis.

Then, the ultrasound scans were assessed for the presence of (1) small hypoechoic lesions in the mediastinum testis, (2) heterogeneous echotexture of lesions, (3) abnormal echogenic band, (4) ductal ectasia, (5) lobulated nodules, and (6) destruction of peripheral parenchyma. About 170 saved ultrasound images were selected and reviewed to meticulously investigate the sonographic findings for a possible classification. Clinical and Para clinical variables were age, bone age, salt losing or simple virilizing presentation, stage of puberty, level of hormonal regulation according to 17-hydroxyprogesterone (17-OHP), androstenedione (ng/mL), and adrenocorticotrophic hormone (ACTH) (pg. /mL).

The results of clinical and laboratory tests were compared to the proposed sonographic classification of TART-RADS. Data were analyzed using SPSS

software (version 22; SPSS Inc., Chicago, IL, USA.). All the statistical exams were performed considering a p-value of less than 0.05 as statistically significant.

The patients were allocated in two groups according to their pubertal state: 1- prepubertal and 2- progressive/complete pubertal state.

3- RESULTS

Overall, 35 children and adolescents with a mean age of 10 years were studied. 16 (46%) patients were in prepubertal state and 19 (54%) were going or had gone through puberty. 33 (94%) patients had

Salt Wasting CAH and 2 (6%) had Simple Virilizing type. Furthermore, 16 patients (46%) had a normal sonogram, and 19 subjects (54%) had one or more sonographic findings of TARTs. The age medians of patients with TARTs and without sonographic findings of TARTs were reported as 13.5 (range: 4-22 years) and 5.9 (range: 8 months-13 years) years, respectively. Overall, in a review of 170 selected ultrasound images of 35 patients, there were five sonographic patterns for testicular lesions (**Fig. 1**). **Table 1** shows the category distribution of the patients.

Table-1: Distribution of patients based on the sonographic classification

Sonographic classification	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
n (%)	16 (46)	7 (20)	8 (23)	3 (8.5)	1 (2.5)
Mean age (year)	5.9 (1-12.5)	9.5 (4-16)	15 (10-22)	14.5 (11-18)	22
Pubertal state* n (%)	4 (25)	3 (43)	8 (100)	3 (100)	1 (100)

*P2G2 Tanner stage and testicular volume of ≥ 4 cc were considered as the start of puberty

There was no significant relation between 17-OHP < 10 or 17-OHP ≥ 10 ng/mL, androstenedione (≤ 3.1 or > 3.1), and ACTH (normal or > 60 pg/ml) with TART classification ($P>0.05$). No considerable difference was observed regarding 17-OHP < 10 or 17OHP ≥ 10 ng/mL, androstenedione (normal or increased), and ACTH (normal or increased) in stage 1 of TARTs in comparison to the other stages ($P>0.05$); however, the frequency of normal androstenedione (87% and 50%) and ACTH (53% and 12.5%) in stage 1 was higher than those reported for the other stages. There was a significant relationship between age and pubertal state with TART staging ($P=0.006$ and $P=0.001$). Also, advanced bone age, a sign of poor long term hormonal regulation, was significantly higher amongst the TART patients ($P=0.028$).

4- DISCUSSION AND CONCLUSION

TART is a rare and benign growth in the testicles mostly occurring in CAH patients. Because of the embryonic origin proximity of the adrenal cortex and testes, it has been proposed that TARTS are the result of adrenal tissue growing in the testes. (6). Although TARTs are benign, compressive effects of the growing lesions may cause testicular damage and infertility (7). Adrenal rest tumors are most commonly observed in testicles; however, studies indicate that they can occur in different parts of the body including celiac plexus, spermatic cord, liver, spinal canal, perirenal tissue, and ovaries (8-13). Many studies have evaluated these lesions in male patients with CAH but studies about its risk factors have not been conclusive (7, 14).

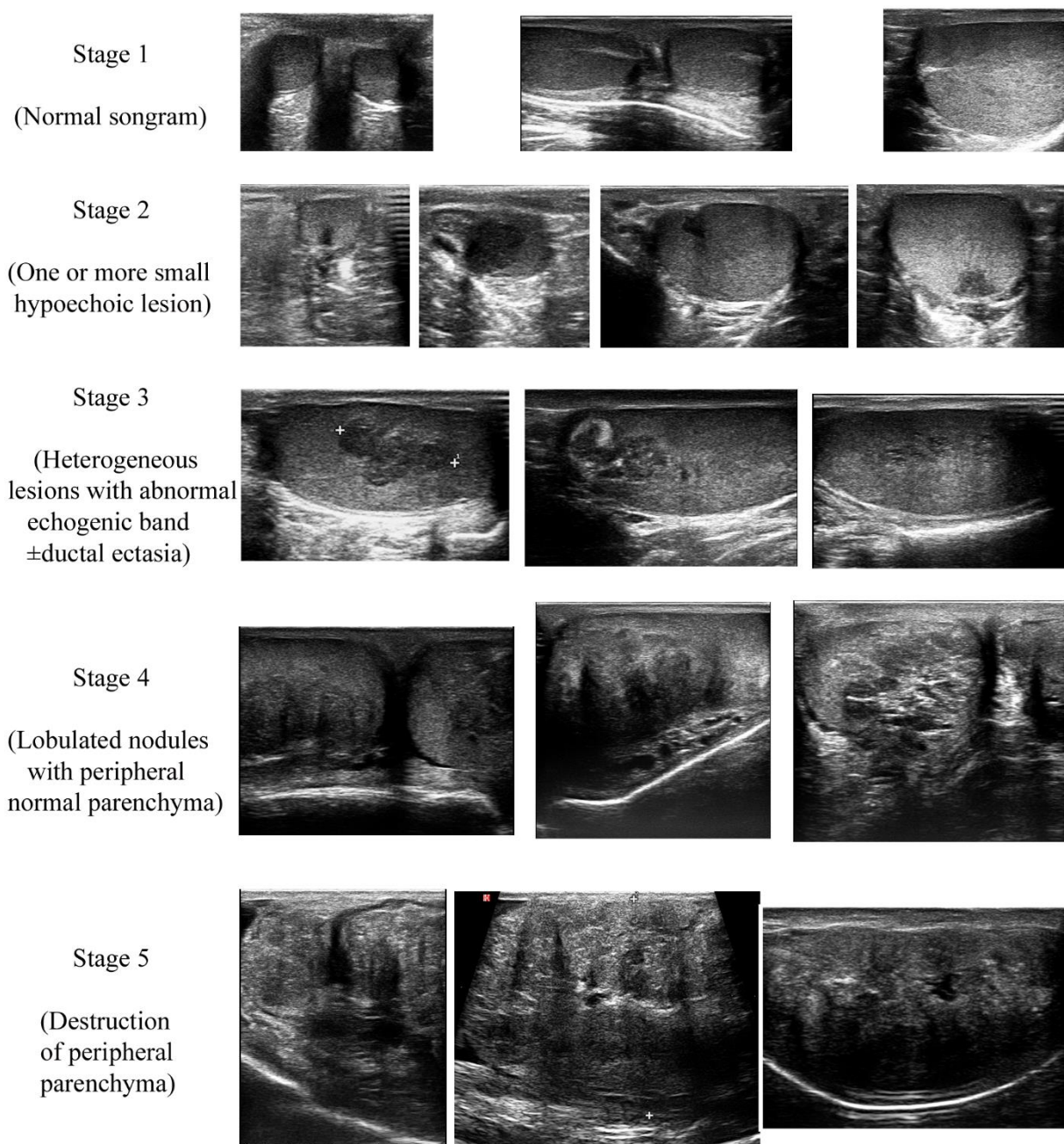


Fig. 1: Testicular adrenal rest tumors-Reporting and Data Systems classification in ultrasound images

Studies have shown different prevalence rates of TART in CAH patients due to differences in patient selection and methods of diagnosis (i.e., palpation and ultrasound) (14-19). In the present study, 54% of the patients had an abnormal sonogram, which is amongst the highest prevalence reported in literature.

Considering its safety, cost efficiency and convenience, ultrasound is usually the first screening method for these lesions. Magnetic resonance imaging (MRI) has been used in some clinical studies and case reports of TART. The MRI characteristics of lesions include hypointensity on T2-weighted images, hyperintensity on T1-

weighted images in most lesions and Homogeneous contrast enhancement on post-contrast T1-weighted images were observed in all lesions (120). Although MRI is effective in confirming the diagnosis, ultrasound is preferred in most studies (7, 21, 22).

Several studies have evaluated the sonographic aspects of TARTs in CAH patients. In this regard, Wang et al. reported 15 cases with the sonographic features of bilateral growing mass near the mediastinum of testicle as a hypoechoic area with rich blood supply (23). A study carried out by Ma et al. evaluated eight patients with TARTs diagnosis. In the aforementioned study, the majority of lesions were on both testes and near the mediastinum. Moreover, most of the lesions had a round or oval shape with a clear border, marked vascularity, and were hypoechoic (24). In a study conducted by Delfino et al., ultrasound showed the presence of TARTs in 11 patients in a total of 18 patients. They explained most lesions as hypoechoic and round, and few lesions with the hyperechoic echotexture and elongated or tubular shape. The lesions showed various vascularity patterns (25).

Yilmaz et al. described the ultrasound and MRI imaging features of TARTs in nine patients with CAH. Ultrasound showed hypoechoic and hypervascular lesions near the mediastinum of testicles in the majority of patients. Most lesions had heterogeneous echotexture (20).

Avila et al. examined 17 intratesticular masses and one extratesticular mass. Most of the lesions were hypoechoic and were located in the mediastinum of the testis. Delfino et al., reported that color Doppler ultrasound showed hypervascularity in six masses, iso vascularity in seven and hypovascularity in five lesions (25, 26). Multiple case reports have also described similar features (27-29).

Several studies have demonstrated that an early diagnosis and treatment would prevent complications in adulthood. Accordingly, scrotal ultrasound screening is recommended every 1-2 years for all male patients with CAH in order to allow for early diagnosis and prevention of late complications, such as infertility (30, 31).

Although these studies have made a review of sonographic findings of TARTs, none of them have proposed a classification for these testicular lesions. In 2009 for the first time, Claahsen-van der Grinten et al. proposed a classic staging of TART based on the histological features of TARTs, parenchyma of testicles, and clinical observations. They categorized the development and growth of TARTs into following five stages:

Stage 1: The presence of adrenal rest cells within the rete testis without pathologic findings in ultrasound

Stage 2: The hypertrophy and hyperplasia of adrenal rest cells becoming visible by ultrasound as one or more small hypoechoic lesions

Stage 3: Further growth of the adrenal rest cells with (reversible) compression of the rete testis

Stage 4: The induction of fibrosis and focal lymphocytic infiltrates; the conflation of several small tumors within the rete testis forming a single lobulated structure separated from the residual testicular tissue by fibrous strands

Stage 5: The irreversible destruction of the testicle

Claahsen-van der Grinten et al. explained that each of these stages is different in prognosis, and each stage may require different clinical approaches. According to this staging system, the optimization of glucocorticoids and surgical removal are required for stage 2 or 3 and stage 4 or 5, respectively. Claahsen-van der Grinten et

al. suggested further studies to validate this classification of TARTs (5).

In the present study, 170 selected ultrasound images of 35 patients were investigated for the assessment of sonographic findings and possibility of a classification system. In addition, the sonographic findings of TARTs in 35 CAH patients diagnosed by biochemical and/or genetic testing were reviewed. Sonographic findings were described in terms of several aspects, including a normal sonogram, presence of a small hypoechoic lesion in mediastinum testis, heterogeneous echotexture of lesions, abnormal echogenic band, ductal ectasia, lobulated nodules, and destruction of peripheral parenchyma. Overall, there were five sonographic patterns for testicular lesions (**Fig. 1**) which are consistent with the histological patterns classified by Claahsen-van der Grinten et al.

Although a study reported the elevation of plasma ACTH levels in TART patients (25), there was no significant abnormality in the hormonal assessment of patients with and without TART in our study. However, the frequency of normal androstenedione and ACTH in stage 1 was higher than those of the other stages. Overall, ultrasound in TART patients showed five discrete sonographic patterns consistent with the histological classifications of Claahsen-van der Grinten et al. These patterns are unique and cannot be achieved by clinical or laboratory tests. The TART-RADS imaging of lesions will allow clinicians to develop more accurate and appropriate approaches.

In addition, testicular involvement with TARTs in about half of the CAH patients indicates the value of ultrasound screening in this population beginning from early childhood in order to prevent the many serious complications, especially infertility. The current study had several strengths and limitations. One of the strong

points of our work is the sample size of 35 patients which is larger than most of the similar studies. However, further investigations are required to validate the consistency of this sonographic TART classification with laboratory tests.

The five-stage classification of sonographic findings of TARTs is matched with histological classifications, including a normal sonogram (stage 1), presence of a small hypoechoic lesion in mediastinum testis (stage 2), heterogeneous echotexture of lesions with an abnormal echogenic band or ductal ectasia (stage 3), lobulated nodules with normal peripheral parenchyma (stage 4), and destruction of peripheral parenchyma (stage 5). Hopefully this TART-RADS imaging of lesions will allow clinicians to develop more accurate and appropriate approaches.

5- ETHICAL CONSIDERATIONS

The current study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the code number of IR.MUMS.MEDICAL.REC.1398.829. And the eligible patients signed informed consent.

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