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RESEARCH LETTER

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An unusual epididymal localization of Testicular Adrenal Rest Tumor in an adolescent with congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder, affecting adrenal cortex steroid synthesis, caused by 21β-hydroxylase (21-OH) deficiency in more than 90% of the cases [1]. The specific mutation of CYP21 gene determines the degree of impairment of 21-OH activity and different phenotypes of CAH: salt-wasting (SW), simple virilizing (SV) and late onset (LO).

One of the most important complication in CAH, above all in males, is a low fertility rate, usually due to testicular adrenal rest tumor (TART) [2]. TART arise from aberrant adrenal tissue which grows in testes prevalently in condition of high ACTH concentration, as it happens in poorly controlled CAH patients [3]. TART is a benign tumor, usually bilateral (75-80%), however it may determine an irreversible damage by compression and toxic-paracrine effects on the surrounding testicular tissue [2, 4]. The prevalence of TART varies between 0 and 94%, reported in both classical CAH phenotypes SW and SV [2–6]. Ultrasound (US) represents the first-line imaging approach in the investigation of TART since it is characterized by low cost, high sensitivity, and non-invasiveness. US is able to identify testicular tumor until minimum measure of ~2 mm in diameter, therefore, it has been proposed to screen males CAH patients to precociously diagnose TART in order to prevent irreversible testicle's damages. Sonographic features of TART include hypoechoic nodules ranging in size, typically located within the mediastinum testis, with increased flow to color-Doppler [7, 8].

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Case presentation

A 15-year-old Caucasian boy was diagnosed with SW CAH because of an adrenal crisis at the age of 1 month and he was treated lifelong with hydrocortisone and fludrocortisone acetate. CAH diagnosis was confirmed by molecular analyses of CYP21A2 gene that revealed compound heterozygous mutation (Intron-2-splice mutation and 8-bp-deletion). He was regularly followed up in Outpatient Clinic of Pediatric Endocrinology, and he underwent periodic biochemical tests (Fig. 1a) and yearly testicular US evaluations. He had a good adherence to therapy associated with regular growth, normal pubertal development, and adequate hormonal and metabolic control until adolescence (since the age of 14) when a progressive deterioration of disease control due to lack of compliance to therapy was reported (Fig. 1a). At the age of 15, physical examination resulted normal; testes volume, evaluated with Prader orchidometer, were 25 ml bilaterally. However, the routine scrotal US examination, performed with a Mindray Resona 9 (Shenzen, China) US machine equipped with a broadband 5–14 mHz linear probe, demonstrated, for the first time, multiple, homogeneous, and well-circumscribed hypoechoic lesions impairing both testes ranging between 3 mm and 9 mm, most of them located along mediastinum testis (Fig. 1b). Power-Doppler showed increased intra and perilesional vascularization, associated with regular and linear caliber of the vessels coursing through the lesions (Fig. 1c). Strain elastography evaluation demonstrated higher stiffness values in all lesions compared to testicular parenchyma (Fig. 1d). Two other nodular lesions were found in both epididymis heads, the greater of which measuring 7 mm in size in the right one. Both epididymal lesions showed the same morpho-structural, power-Doppler, and elastographic features of testicular small masses (Fig. 1b–d).

MRI examination confirmed US findings, demonstrating slight hyperintensity on T1 Weighted images (WI), low

a

Age (years)		12.7	13.7	13.9	14.3	15 *	15.3	15.8	N
ACTH (pg/ml)		113	>1250	488	827	1057	440.7	430	6 - 40
17-OHP (ng/ml)		14.9	43.6	44	89	87	33	27	0.3 - 2.2
Delta4-A (ng/ml)		0.8	15.1	4.5	8	17	8	7.6	0 - 2.9
Renin (uUl/ml)			35.9	43.1	16.5	16.9	13.5	14.4	3.6 - 20
Testicular volume (ml)	Right					24.5		24.3	
	Left					22.8		22.3	

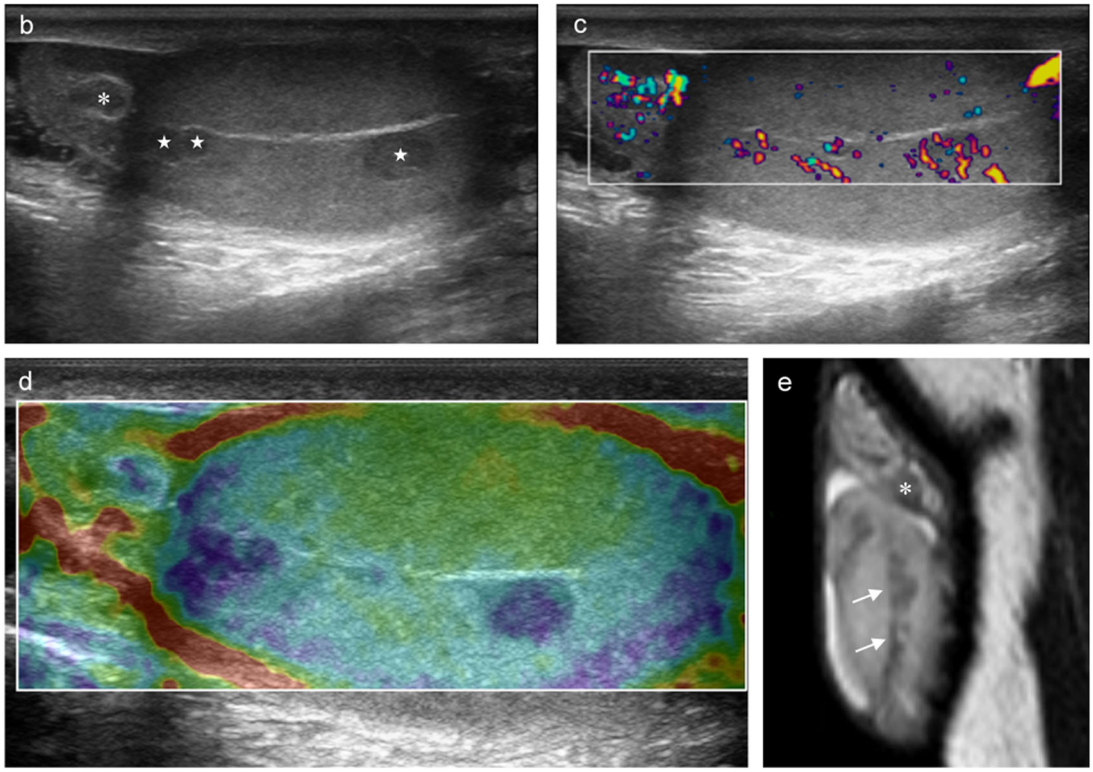

Fig. 1 **a** follow-up of laboratory tests and testicular volume at ultrasound [TART diagnosis (*), normal hormonal range (N), 17-hydroxyprogesterone (17-OHP), Delta4-androstenedione (Delta4-A)]. **b** b-mode ultrasonography image of the right testis; **c** Power-Doppler ultrasonography image of the right testis; **d** Strain Elastography ultrasonography image of the right testis; **e** T2W MRI image of the right testis. Images showed multiple intratesticular solid masses, located along the mediastinum testis (stars in **b** and arrows in **e**) and a single mass into the head of epididymis (astersisk in **b** and **e**)

intensity signal on T2-WI (Fig. 1e), with no restricted diffusion in diffusion weighted imaging (DWI), in both testicular and epididymal lesions.

Eight months after TART's diagnosis and about 6 months after patient restarted glucocorticoid therapy, a reduction in size of testicular and epididymal lesions was documented at US. In particular, in the right testis the largest lesion decreased from 9 mm to 7 mm, while in the left one a complete regression of the lesions was demonstrated with the exception of one stable lesion measured 5 mm. Epididymal lesion was decreased in size in the right epididymis (from 7 mm to 5 mm), while it remained unmodified in the left one. Testicular volume remained stable during the follow-up (Fig. 1a).

Moreover, tumor markers (alpha-fetoprotein, beta-HCG, and carcinoembryonic antigen) were persistently negative.

Discussion

To the best of our knowledge, this is the first case of unusual epididymal localization of TART associated with typical testicular localization reported in a SW CAH patient. It is speculated that adrenal cells, derived from the coelomic epithelium, descend in the scrotum during the eighth week of gestation adhered to precursor of gonadal tissues [4]. We hypothesized that the migration of adrenal cells through the efferent ductules could explain the unusual localization of TART in the epididymal head.

TART is one of the most important causes of infertility in CAH males. Diagnosis of TART is based mainly on clinical features such as under-treated CAH male with hypercorticotropinemia and tumor mass reduction or arrest of growth after glucocorticoids therapy adjustment, and US findings

including hypoechoic nodules located bilaterally within the mediastinum testis, increased flow to color-Doppler, clear delineation from the testicular parenchyma [7, 9, 10]. All these features were observed in our patient, in which, besides, an unusual bilateral epididymal localization was demonstrated.

Prompt non-invasive diagnosis of TART should be performed in order to prevent testicle's damages and unnecessary biopsies or orchidectomies. US is considered the first imaging approach to diagnose TART, therefore, CAH male should undergo periodically to testicular US screening, as previously suggested [3, 9, 10].

Few reports are available on imaging features of TART [7, 11, 12]. Wang et al. [7], in the largest available pediatric cohort of CAH male with TART (15 patients), reported the following US peculiarity of TARTs: bilateral localization adjacent to the testicular mediastinum (100%), clear delineation from the testicular parenchyma (100%), hypoechogenicity (93.4%), rich vascularization with regular vessels caliber (76.7%). The latter feature has been reported also by other authors as a peculiar aspect of TARTs compared to other testicular tumors [10, 13].

Notwithstanding the typical features of TART, differential diagnosis includes Leydig cell tumor (LCT) and malignant testicular tumors (MTT), in particular germ cell tumor that can occur approximately at the same age of TART. Differently from TART, LCT, and MTT are usually unilateral, located anywhere in the testis and characterized by mixed echogenicity [14]. However, US exhibits low specificity in differentiating between benign and malignant intratesticular lesions since it provides only structural information [15], therefore the combination of clinical characteristics, strict US follow-up, and a multiparametric US approach with color-power Doppler US and Strain Elastosonography can provide further information to improve the non-invasive diagnostic accuracy of the testicular masses [16–18].

Elastography provide information concerning tissue elasticity. Testicular parenchyma shows homogeneous and hard stiffness in the color scale elasticity imaging [19], and focal lesions appear harder compared to parenchyma, as it happens for TART [19]. However, elastography, as a single US modality, shows a low specificity rate, therefore it should represent a complementary evaluation in the contest of a multiparametric US evaluation, as suggested by Pozza et al. [17] who concluded that elastography may support grayscale US in differentiating non-palpable testicular malignancies from non-neoplastic lesions, and by Auer et al. [14] that demonstrated a very high sensitivity and specificity rates by combining strain elastography and contrast-enhanced US in differentiating testicular lesions.

MRI has been proposed as additional diagnostic procedure in differential diagnosis of testicular lesions, characterized by high sensitivity and specificity [20, 21]. Manganaro et al. [20], in a prospective series of patients, reported a 93% diagnostic accuracy of MRI in differential diagnosis between malignant and benign testicular masses, highlighting that a markedly hypointense signal on T2-Weighted sequences is significantly associated with a benign nature of the lesion.

In our case, the findings of well-defined margins and hypointense signal of the lesions on T2-WI supported the diagnosis of TART, as previously suggested [22].

Notwithstanding the high diagnostic accuracy of multiparametric US, testicular biopsy remains the gold standard methods for differential diagnosis of testicular lesions; however, our patients did not undergo biopsy to confirm TART histologically since the features of the lesions at multiparametric US, their localization bilaterally in the mediastinum testis in a poor controlled pubertal CAH male, and the reduction in size after glucocorticoids therapy restarting, are, as a whole, strong suggestive for TART.

In conclusion, this is the first documented case of epididymal localization of TART in an adolescent with SW CAH. TART has typical features at multiparametric US, therefore, in CAH male, in presence of testicular lesions appear bilateral, hypoechoic, hard, clearly delineated, rich and regular in vascularization, localized close or inside the hilum, the diagnosis of TART should be always considered and an epididymal localization should be encountered. In those patients, testicular US screening should be performed regularly, at least every two years in early childhood and annually in the peripubertal period, or even more frequently in patients with lack of compliance to glucocorticoids therapy.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from patient included in the clinical report and from their parents.

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. H.L. Claahsen-van der Grinten, A.R. Hermus, B.J. Otten, Testicular adrenal rest tumours in congenital adrenal hyperplasia. Int. J. Pediatr. Endocrinol. **2009**, 624823 (2009)
2. H. Falhammar, H.F. Nystrom, U. Ekstrom, S. Granberg, A. Wedell, M. Thoren, Fertility, sexuality and testicular adrenal rest

tumors in adult males with congenital adrenal hyperplasia. Eur. J. Endocrinol. **166**, 441–449 (2012)
3. D. Corica, S. Santucci, E. Pitrolo, M. Romeo, M. Wasniewska, F. De Luca, Testicular adrenal rest tumor in an adolescent with congenital adrenal hyperplasia, resolved by therapy doses adjustment. Minerva Pediatr. **66**, 233–235 (2014)
4. H.L. Claahsen-van der Grinten, F.C. Sweep, J.G. Blickman, A.R. Hermus, B.J. Otten, Prevalence of testicular adrenal rest tumors in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Eur. J. Endocrinol. **157**, 339–344 (2007)
5. E.D. Cakir, F.S. Mutlu, E. Eren, A.O. Paşa, H. Sağlam, O. Tarim, Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia. J. Clin. Res. Pediatr. Endocrinol. **4**, 94–100 (2012)
6. H.L. Claahsen-van der Grinten, B.J. Otten, F.C. Sweep, P.N. Span, H.A. Ross, E.J. Meuleman et al. Testicular tumors in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency show functional features of adrenocortical tissue. J. Clin. Endocrinol. Metab. **92**, 3674–3680 (2007)
7. Z. Wang, Z. Yang, W. Wang, L.D. Chen, Y. Huang, W. Li et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine **94**, e1471 (2015)
8. S.S. Deshpande, D. Shetty, S. Saifi, Sonographic appearance of testicular adrenal rest tumour in a patient with congenital adrenal hyperplasia. Pol. J. Radiol. **82**, 526–529 (2017)
9. Z. Aycan, V.N. Bas, S. Cetinkaya, S. Yilmaz Agladioglu, T. Tiryaki, Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clin. Endocrinol. **78**, 667–672 (2013)
10. N.M. Stikkelbroeck, H.M. Suliman, B.J. Otten, A.R. Hermus, J.G. Blickman, G.J. Jager, Testicular adrenal rest tumours in postpubertal males with congenital adrenal hyperplasia: sonographic and MR features. Eur. Radiol. **13**, 1597–1603 (2003)
11. N.A. Avila, T.S. Shawker, J.V. Jones, G.B. Cutler Jr, D.P. Merke, Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR Am. J. Roentgenol. **172**, 1235–1238 (1999)
12. D. Lee, S.K. Rodgers, Testicular adrenal rests. Ultrasound Q. **24**, 105–107 (2008)
13. N.A. Avila, A. Premkumar, T.H. Shawker, J.V. Jones, L. Laue, G. B. Cutler Jr., Testicular adrenal rest tissue in congenital adrenal hyperplasia: findings at Gray-scale and color Doppler US. Radiology **198**, 99–104 (1996)
14. T. Auer, T. De Zordo, C. Dejaco, L. Gruber, R. Pichler, W. Jaschke et al. Value of multiparametric US in the assessment of intratesticular lesions. Radiology **285**, 640–649 (2017)
15. C. Cicero, M. Bertolotto, B.R. Hawthorn, C. Trambaiolo Antonelli, P.S. Sidhu, G. Ascenti et al. Multiple, synchronous lesions of differing histology within the same testis: ultrasonographic and pathologic correlations. Urology **121**, 125–131 (2018)
16. D.Y. Huang, P.S. Sidhu, Focal testicular lesions: colour Doppler ultrasound, contrast-enhanced ultrasound and tissue elastography as adjuvants to the diagnosis. Br. J. Radiol. **85**, S41–S53 (2012). Spec No 1
17. C. Pozza, D. Gianfrilli, G. Fattorini, E. Giannetta, F. Barbagallo, E. Nicolai et al. Diagnostic value of qualitative and strain ratio elastography in the differential diagnosis of non-palpable testicular lesions. Andrology **4**, 1193–1203 (2016)
18. P.S. Sidhu, Multiparametric ultrasound (MPUS) imaging: terminology describing the many aspects of ultrasonography. Ultraschall Med. **36**, 315–317 (2015)
19. G. Jedrzejewski, I. Ben-Skowronek, M.M. Wozniak, A. Brodzisz, E. Budzynska, A.P. Wieczorek, Testicular adrenal rest tumors in boys with congenital adrenal hyperplasia: 3D US and elastography–do we get more information for diagnosis and monitoring? J. Pediatr. Urol. **9**, 1032–1037 (2013)
20. L. Manganaro, V. Vinci, C. Pozza, M. Saldari, D. Gianfrilli, R. Pofi et al. A prospective study on contrast-enhanced magnetic resonance imaging of testicular lesions: distinctive features of Leydig cell tumours. Eur. Radiol. **25**, 3586–3595 (2015)
21. L. Manganaro, M. Saldari, C. Pozza, V. Vinci, D. Gianfrilli, E. Greco et al. Dynamic contrast-enhanced and diffusion-weighted MR imaging in the characterisation of small, non-palpable solid testicular tumours. Eur. Radiol. **28**, 554–564 (2018)
22. R. Yılmaz, D. Şahin, A. Aghayev, O.B. Erol, Ş. Poyrazoğlu, N. Saka et al. Sonography and magnetic resonance imaging characteristics of testicular adrenal rest tumors. Pol. J. Radiol. **82**, 583–588 (2017)