



Congenital Anomalies/Anatomical Variants

Testicular Adrenal Rest Tumors (TARTS) With Unusual Histological Features in Congenital Adrenal Hyperplasia (CAH)

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ABSTRACT

Congenital adrenal hyperplasia (CAH) patients with testicular adrenal rest tumors (TARTs) with testicular enlargement present a serious diagnostic challenge. According to the data TARTs are usually benign. They are rare, resulting in paucity in the medical literature regarding their pathological features. We report a case of bilateral synchronous mass-forming TARTs with marked cytological and nuclear atypia misinterpreted as malignant testicular tumors in a 40-years-old man with CAH and CT and MRI data for pheochromocytoma of the right adrenal gland and paraaortal and paracaval lymphadenomegaly. He was previously diagnosed with adrenal cortical carcinoma of the left adrenal gland.

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Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by CYP 21(21-hydroxylase) deficiency. Testicular adrenal rest tumors (TARTs) are a complication of CAH, stimulated by the hypersecretion of adrenocorticotrophic hormone (ACTH). These lesions within the rete testis are bilateral, synchronous, nodular and multiple. TARTs lead to structural damage, spermatogenesis disorders, infertility, forming lesions that could be mistaken for Leydig cell tumor (LCT).¹ At present, the etiology of TARTs is unclear. Among the considered origins are: adrenal rests, interstitial cells, and pluripotent cells of the testicular stroma stimulated by elevated ACTH levels.

Case presentation

We report a case of a 40-year-old man with CAH/21-hydroxylase deficiency, who willingly interrupted Prednisolone therapy for years. In 2007 his left adrenal gland was removed and diagnosed with adrenocortical carcinoma. In 2012 CT scan (Fig. 1) showed a tumor in the right adrenal gland, confirmed in 2013 by MRI, with

retroperitoneal lymphadenomegaly. Serum hormonal screening showed high 17-OH progesterone and ACTH. The patient refused operation.

He was referred to us from another hospital because of a synchronous progressive enlargement of bilateral testicular masses during substitutive medical therapy (Fig. 2). Serum tumor markers at 12.09.2013: AFP 10.56 IU/mL (AFP 4.03 IU/mL 01.2012), hGT beta and CEA – not elevated, semen analyses: azoospermia.

Considering the possibility of malignant testicular neoplasm, the patient underwent bilateral orchiectomy, because the frozen sections were interpreted as malignant tumors. Gross findings: right testicle 2.5/2.5/2.5 cm, left – 3.5/2/2 cm, with brown firm cut surface, lobulated and septated by yellow folds (0.1–1.5 cm).

The microscopic examination showed complete replacement of the normal testicular tissue by sheets and nests of large bizarre mono- and multinucleated cells, large nuclei with prominent nucleoli, abundant eosinophilic cytoplasm with lipochrome pigments (Fig. 3). Nests of cells were separated by fibrous septa. Only the epididymis and a thin band of atrophic testicular parenchyma were preserved.

The tumor cells did not express CD 117, PLAP, CK. Melan A and inhibin- α were positive in 50% of the cells. There were no mitotic figures on HE-staining (Ki 67 negative). No vascular invasion and tumor emboli were found. The spermatic cord and tunica vaginalis were not infiltrated.

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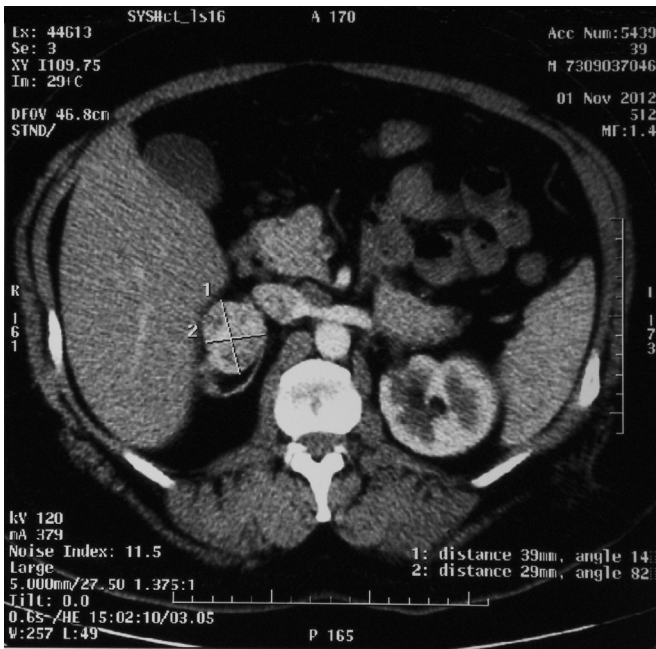


Figure 1. CT-scan showing a tumor formation in the right adrenal gland. Dimensions: 39/29 mm.

We excluded primary germ cell testicular tumors and anaplastic large cell lymphoma, metastatic nonsecreting pheochromocytoma. “TARTs” was the appropriate diagnosis. There was still suspicion for metastatic adrenocortical carcinoma because of the CT and MRI findings. In order to prove the diagnosis the patient agreed to the surgical removal of his right adrenal gland in 01.2014. Adrenocortical carcinoma was histologically diagnosed again at other hospital.

We revised all slides and performed immunohistochemical analyses. In the left adrenal gland we found polygonal cells with mild nuclear pleomorphism, conspicuous nucleoli, abundant eosinophilic granular cytoplasm, some with lipochrome pigments, without mitotic activity (Ki 67 positive in <1% of nuclei). The clear cell component was about 26%. In CAH, marked diffuse hyperplasia of zona fasciculata is a result of ACTH stimulation. There is also a

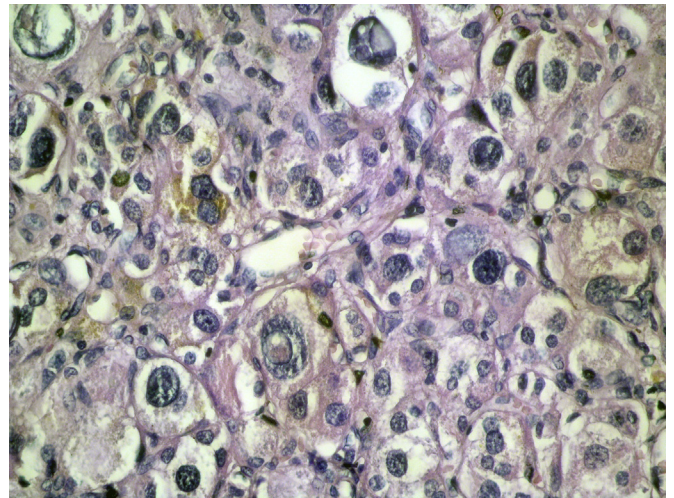


Figure 3. Adrenal tissue, bizarre cells with eosinophilic granular cytoplasm and large hyperchromatic nuclei with pseudoinclusions, binucleated cells (hematoxylin-eosin, $\times 400$).

conversion of zona fasciculata cells into zona reticularis-type cells (lipid-depleted). The cells exhibited strong positive expression for vimentin, Melan A and inhibin. In the right adrenal gland microscopically we found fields and circumscribed but nonencapsulated nodules that protruded into the adjacent fat, consisting of fasciculata-type cells and nodules composed of zona reticularis-type cells with lipofuscin. Nuclear and cellular pleomorphism was more prominent than in the left adrenal gland. Mitoses necrosis, hemorrhage, sinusoidal, vascular and capsular invasion were not found. The required number of morphological criteria, according to Weiss and Aubert, to classify the lesion as carcinoma, were not met.²

Revised diagnosis: CAH bilateral adrenal cortical hyperplasia of a diffuse and nodular type with multiple bilateral cortical nodules, pigmented nodules and congenital adrenal cytomegaly and bilateral TARTs revealing morphologically similar changes.

Discussion

Unfortunately, several oversights were done during the therapy. TARTs should be our first hypothetic diagnosis as many patients with CAH have this condition. They are a well-known complication in males with CAH (reported prevalence of up to 94%).³ The initial histological diagnosis of adrenal cancer of the left gland was misleading, which pushed the diagnostic process and treatment in the wrong direction—as for a malignant case.

Recognition of the TART entity is essential when evaluating young males with testicular masses.⁴

Ectopic adrenal tissue frequently develops at testicular level. It is identical to that of the adrenal gland and its functionality can be stimulated by ACTH and suppressed by glucocorticoid therapy. Color Doppler may be helpful in establishing the diagnosis.⁵ Our patient was not followed-up strictly – he followed consecutive replacement therapy until his 18th year. After that he interrupted therapy at his own discretion. He admits that while on corticoid therapy the gonads become almost normal on consistency and size, while in periods without treatment they become hard and bigger, perfectly corresponding to the possible diagnosis of TART.

The absence of gonad dysfunction in a group of children in a trial suggests that gonad dysfunction, as frequently reported in adult CAH patients with TART, develops after childhood.³ Our patient reports for testicle enlargement after the age of 30.

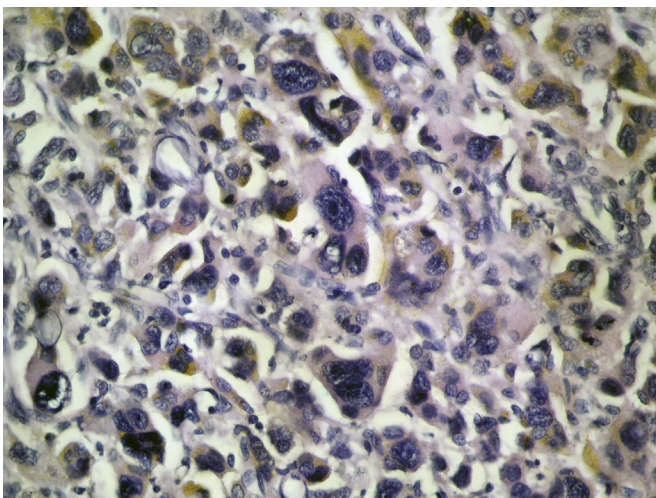


Figure 2. Testicular tissue, large bizarre mono- and multinucleated cells, large nuclei with prominent nucleoli, abundant eosinophilic cytoplasm with lipochrome pigments (hematoxylin-eosin, $\times 400$).

The occurrence of TARTS is a sign of bad control of the CAH disease. Various genotypes are also found in patients with and without TARTS. It is mandatory to perform prophylactic ultrasonographies of the testicles in patients with CAH.

The doctors involved in the treatment agreed to change the initial diagnosis from malignant tumors of the adrenals and testicles to CAH with TARTS. The patient is on replacement therapy and intensive follow-up.

Conclusion

The benign course of the clinical development of the disease and the present condition of the patient gives us the right to accept the diagnosis of TARTS as fully reasonable. We will draw the attention of the clinicians to the presence of the TARTs and to evaluate critically every patient with testicular tumors concomitantly with CAH. The multidisciplinary approach with the involvement of endocrinologist, pathologist and urologist is of crucial importance for the correct diagnosis.

Conflict of interest

The authors hereby declare that there is no conflict of interest.

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