CASE REPORT

Unusual Presentation of Simple Virilising Congenital Adrenal Hyperplasia as a Testicular Adrenal Rest Tumor

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Published: 22 November 2014
Ibnosina J Med BS 2014;6(6):313-317
Received: 06 June 2014
Accepted: 18 July 2014
This article is available from: http://www.ijmbs.org

Abstract
Testicular adrenal rest tumors are commonly seen in congenital adrenal hyperplasia. The tumors are typically bilateral and arise from ACTH dependent aberrant adrenal cells in the testes. Diagnosis is clinically confirmed by ultrasound imaging. These tumors are characterized by their response to steroid replacement and biopsy is not routinely required. Differentiating the tumor from Leydig cell tumor can be difficult. Management and prognosis for these two pathologies are different, so extensive investigations may be required to confirm the diagnosis. We present a 5 year old boy who had an unusual presentation of a testicular tumor and detail the investigations undertaken to differentiate a testicular adrenal rest tumor from a Leydig cell tumor.

Key words: Congenital adrenal hyperplasia (CAH), testicular adrenal rest tumor (TART), Leydig cell tumor, Synoptophysin

Introduction

Testicular adrenal rest tumors (TART) in patients with CAH were first described by Wilkins in 1940 (1). Now with the use of ultrasound, their prevalence in CAH is common (2). It is hypothesized that TART arises from aberrant adrenal cells that descend with the testes during embryonic development and can be seen in normal male infants (3). The tumors form under influence of raised ACTH levels acting on aberrant cells. Ultrasound scan is the method of choice for detection of TART because it is readily available and enables small tumors to be detected (4). In one study, TARTs were detected in 16 out of 17 patients with CAH in whom only 6 were palpable (5). An adrenal rest tumor can clinically mimic a Leydig cell tumor, leading to unnecessary orchidectomy. A correct diagnosis is essential as a Leydig cell tumor is potentially malignant. Although TART may resemble a Leydig cell tumor histologically, the former contains sheets, nests, and cords of cells with abundant eosinophilic cytoplasm. These cells may contain

lipochrome pigment, but Reinke crystalloids, characteristic of Leydig cells, are absent. TART also shows features of low mitiotic activity, extensive fibrosis, lymphoid aggregates, adipose metaplasia and prominent lipochrome. In addition to histology, immunohistochemistry may be a distinguishing feature (6).

Case report

Presentation

We report a 5 year old boy who was referred with a suspected testicular tumor. At 4.5 years, examination revealed genital staging of G4 and a pubic hair of PH 3 (Fig. 1). Testicular size was 4 and 2 ml for the right and the left sides, respectively. Both testes were of normal

Figure 1. Appearance of genitalia with features of precocious puberty

consistency and there was no discrete mass palpable in the right testis. Growth velocity was accelerated at 10cm/yr. He was normotensive and the rest of the examination was normal.

Investigations

Initial investigations showed an early pubertal level of testosterone (1.5 nmol/L), but prepubertal levels of gonadotrophins. In contrast, serum 17OH-progesterone (17OHP) was markedly elevated at 426 nmol/l (NR 0.6-6.8 nmol/ml). Tumor markers; hCG and alpha fetoprotein were negative. Bone age was 11 years at a chronological age of 5 years. Ultrasound of the testes revealed a hypoechoic diffuse, irregular inhomogenous lesion at the upper

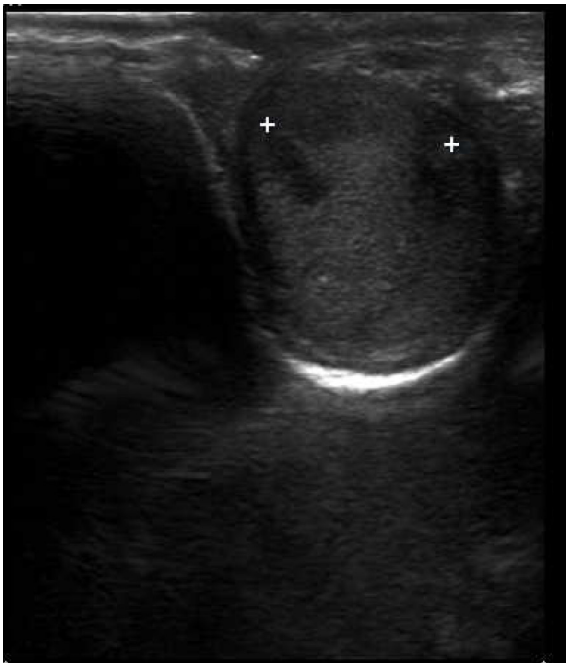

Figure 2. Sagittal sonogram of the right testis demonstrating multiple hypo echoic intra testicular infiltrates at the upper pole extending from the hilar region toward the center of the testis.

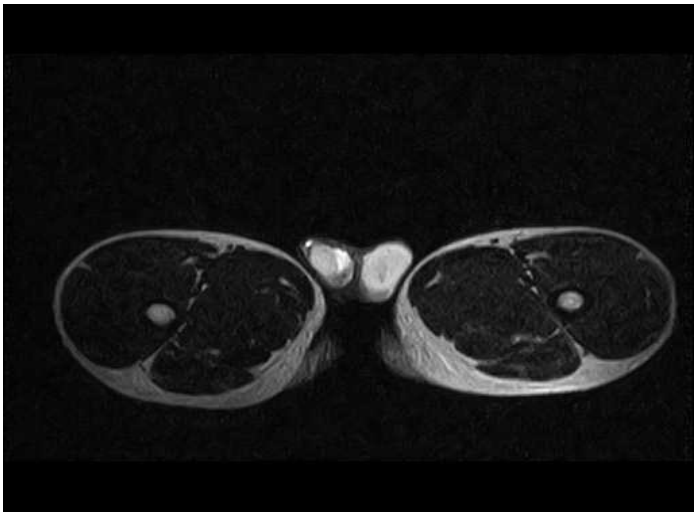

Figure 3. Axial T2 MRI scan demonstrating small hypo intense foci near the testicular hilar zone with hypo intense infiltrates at the upper pole of the right testis at the posterior zone.

pole of the right testis measuring 1.2 x 0.98 cm (Fig 2). There was no calcification or appreciable vascularity on complementary Doppler workup. MRI showed multiple hypoechoic intratesticular infiltrates at the upper pole extending from the hilar region towards the center of the testis, the largest measuring 12x9 mm diameter (Fig 3). In view of the elevated 17OHP level, a sequencing screen of the CYP21A2 gene was performed. It tests for gene

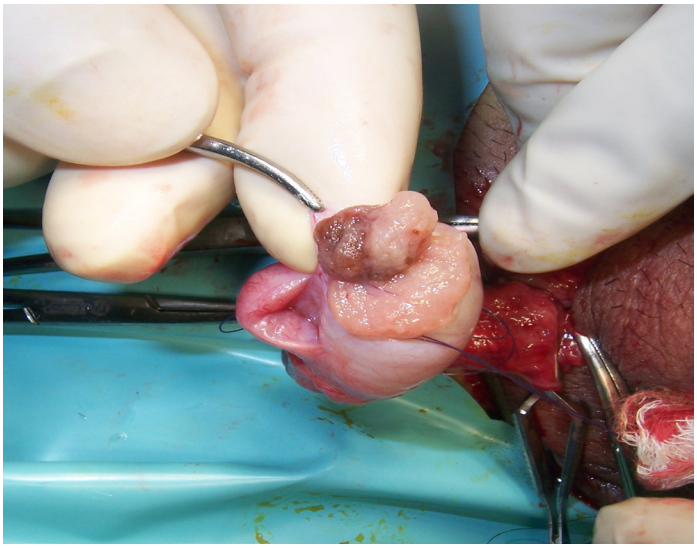

Figure 4. Macroscopic appearance of TART prior to biopsy

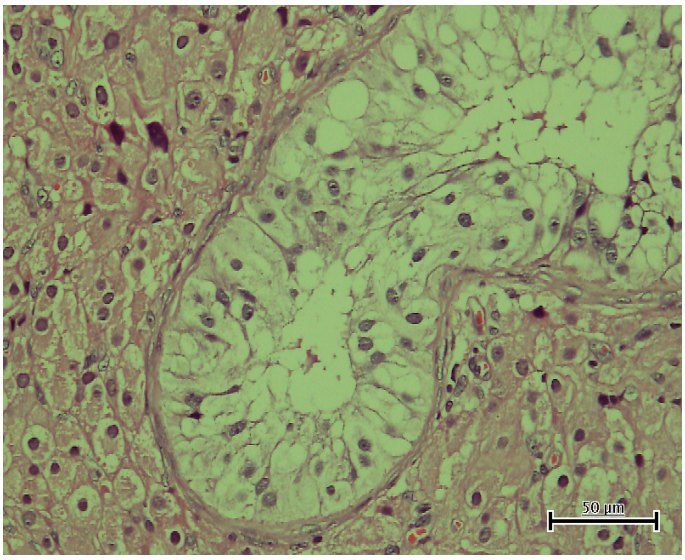

Figure 5. Hematoxylin and Eosin stain showing seminiferous tubules surrounded by cells arranged in sheets, nests and cords with abundant eosinophilic cytoplasm.

copy number, gene to pseudogene conversion, 7 common point mutations and the exon 6 cluster of mutations. This sequencing screen detects about 90% of mutations causing 21-hydroxylase deficiency. In this particular case, no mutation was identified.

Treatment and further investigations

The clinical diagnosis was consistent with simple virilising CAH associated with a unilateral TART. Treatment with hydrocortisone, 12 mg/m^2/day in three divided doses, was started to suppress the 17OHP level. Six months later, serum

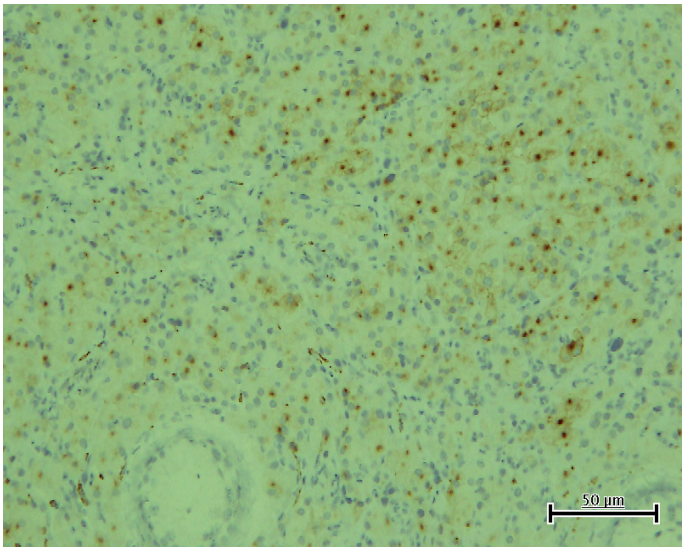

Figure 6. Immunohistochemistry showing strong uptake of Synoptophysis stain.

17OHP had decreased to 46 nmol and a repeat ultrasound showed a reduction in the size of the testicular mass to 0.6 X 0.6 cm. Since TART is usually bilateral, a biopsy of the right testis was performed to exclude a Leydig cell tumor. Macroscopically, a mass measuring 1.2 x 0.7 cm in aggregate with brownish nodular homogenous cut surface was seen at the upper pole of the right testis (Fig. 4). On histology, the tumor cells had well-defined outlines with deeply acidophilic but occasionally clear cytoplasm, and a round or oval nuclei. The cells were arranged in sheets, nests, and cords with abundant eosinophilic cytoplasm and contained lipochrome pigment. Reinke crystalloids were absent. The mass lacked fibrous bands, atypia, necrosis and mitosis. The seminiferous tubules were surrounded by the lesion (Fig. 5). Immunohistochemistry staining using Synoptophysin showed strong diffuse reactivity (Fig. 6).

Outcome and follow-up

Puberty had progressed further with an LHRH stimulation test demonstrating gonadotrophin -dependent precocious puberty. Consequently, treatment with a gonadotrophin analogue was started at the age of 7 years.

Discussion

Diagnosis in this child presented a clinical dilemma because of some unusual features. The diagnosis of CAH was only made after presenting with a testicular mass consistent with TART. Generally, a diagnosis of CAH is already known prior to the detection of the testicular tumors. However, there are reports where detection of the tumor has led to the diagnosis of CAH (7). CAH in this

case was not of classical type which is usual in association with TART. Furthermore, the tumor was unilateral, whereas in 14 reported cases of TART, the tumors were found to be bilateral in 13 (6). A five stage classification for TART whereby the adrenal rest cells are initially only confined to the rete testis and not visible radiologically may explain the unilateral presentation of the tumor (8). It was expected that one of the common mutations causing 21-hydroxylase deficiency would be found when the CYP21A2 gene was screened. It is possible he has one of the rare mutations but only extensive whole gene sequencing would confirm whether that was the case. An alternative explanation may be 11beta-hydroxylase deficiency, although 17OHP levels in this enzyme deficiency are only mildly elevated. Despite these caveats, the clinical features are strongly in favor of TART associated with CAH. He presented with virilisation and rapid growth, advanced bone age an increased serum testosterone and a markedly elevated 17OHP level. The 17OHP response to steroid replacement and the reduction in tumor size are in keeping with the diagnosis of CAH. Since the testicular mass was unilateral in this case, it was important to exclude an alternative explanation such as a Leydig cell tumor. Histology showed no Reinke crystalloids and immunohistochemistry was consistent with TART based on strongly-positive staining with Synaptophysin (9). Performing a testicular biopsy was justified as invariably, TART presents as a consequence of known CAH and in bilateral form (10). The management of this boy centred primarily on clinical indices with the balance of probabilities suggesting the unilateral testis mass was due to TART in association with CAH. The exception, rather than the rule, underlies some of the unique aspects of this case and its management.

Learning points

- Testicular adrenal rest tumor can present unilaterally and pose a diagnostic challenge to differentiate from a Leydig cell tumor.
- Testicular adrenal rest tumor can be the presenting feature of simple virilising congenital adrenal hyperplasia.
- Clinical indices and the response to steroid replacement are key features in the differential diagnosis.
- Histology and Synaptophysin immunohistochemistry are essential components to exclude a Leydig cell tumor when the testis mass is unilateral.
- Whole gene sequencing for less common mutation causing congenital adrenal hyperplasia (CAH) might be considered in unusual clinical presentation of CAH.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or non-profit sector.

Declaration of interest

The authors report no conflict of interest.

Patient consent

Written informed consent was obtained from the patient's father for publication of the submitted manuscript and accompanying images.

Author contributions and acknowledgements

Asma Deeb is the patient's physician. She wrote the manuscript and coordinated other contributions from the co-authors. Aziz Khan performed a number of investigations while Amin Gawhary, Muhand Shakir and Emad Mussa reported on the surgical, histological and radiological parts of the manuscript, respectively. Ian Hughes coordinated the genetic studies and edited the final version of the manuscript.

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