A 14-Year-Old Saudi Boy with Gynecomastia, Cushing Syndrome, Large-Cell Calcifying Sertoli Cell Tumor of the Testis, and Carney Complex

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Conflict of interest:
None declared

Patient:
Male, 14-year-old

Final Diagnosis:
Carney complex

Symptoms:
Gynecomastia • testicular pain

Medication:
—

Clinical Procedure:
Invasive adrenal venous sampling

Specialty:
Endocrinology and Metabolic

Objective:
Rare disease

Background:
Carney complex (CNC) is a rare multiple neoplasia syndrome with autosomal dominant inheritance. CNC is frequently misdiagnosed owing to its diverse clinical characteristics. We reported the case of a 14-year-old Saudi boy with a history of gynecomastia, Cushing syndrome, large-cell calcifying Sertoli cell tumor of the testis, and CNC.

Case Report:
The patient was referred to the pediatric endocrine clinic for evaluation of bilateral slow progressing gynecomastia for 1-year duration. His clinical examination revealed lentigenes, bilateral diffuse breast enlargement (consistent with Tanner stage III), and asymmetrical testicular enlargement, more on the left side. Other systemic examinations were unremarkable. The initial blood workup showed elevated estradiol level with unsuppressed cortisol after an overnight 1-mg dexamethasone suppression test. Breast ultrasound (US) confirmed true gynecomastia. Testicular US revealed microcalcification and the testicular biopsy confirmed diagnoses of large-cell calcifying Sertoli cell tumor (LCCSCT). A 2-step dexamethasone suppression test showed a paradoxical rise in serum and urine cortisol levels, which are characteristic for PPNAD. LCCSCT and PPNAD are 2 major criteria fulfilling a diagnosis of CNC. The gene test showed heterozygous mutation in the PRKAR1A gene, which is diagnostic for CNC. The patient underwent bilateral mastoplasty and was planned for radical left orchiectomy.

Conclusions:
Gynecomastia and LCCSCT can be presenting features of CNC, which mandates careful, thorough clinical examination and tailored investigation to reach a diagnosis.

Keywords:
Carney Complex • Sertoli Cell Tumor

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/937404
Background

Carney complex (CNC) is a rare genetic disorder involving multiple neoplasia syndrome, first described in 1985 [1]. More than 50% of cases are familial owing to an autosomal dominant inheritance pattern, or appear occasionally as a result of a de novo genetic defect [2].

The pathogenesis of PPNAD is unclear, but it appears to be associated with pathogenic variants of the PRKAR1A gene [3]. CNC is inherited in an autosomal dominant pattern with high penetrance but a heterogeneous expression [4]. Approximately one-quarter of cases are due to de novo mutations. There are 2 genetic sites that have been associated with CNC. Inactivating mutations in the protein kinase A type I-alpha regulatory subunit (PRKAR1A) gene on chromosome 17q22-24 are found in most CNC patients [5]. A second locus on chromosome 2p16 is also associated with CNC [6]. Cushion syndrome is the most frequently observed endocrine tumor in CNC, occurring in approximately 25% of affected individuals. Large-cell calcifying Sertoli cell tumors (LCCSCTs) are observed in one-third of affected males within the first decade of life and in most adult males. Up to 75% of individuals with CNC have multiple thyroid nodules, most of which are nonfunctioning thyroid follicular adenomas. Clinically evident acromegaly from a growth hormone (GH)-producing adenoma occurs in approximately 10% of adult patients. Psammomatous melanotic schwannoma (PMS), a rare tumor of the nerve sheath, occurs in an estimated 10% of affected individuals. The median age at diagnosis is 20 years. The diagnosis of CNC is established in a proband with 2 or more major diagnostic criteria and/or by identification of a heterozygous germline pathogenic variant in PRKAR1A on molecular genetic testing [7,8]. It has been observed that most CNC patients (>80%) have spotty skin pigmentation or skin growths, which usually emerge early in life and can occur anywhere on the body, classically on the mucosa, lips, face, and genital region [2]. Nevertheless, the majority of non-cutaneous lesions found in CNC are cardiac myxomas, accounting for over 50% of CNC-related deaths [9-11].

Case Report

A 14-year-old boy was referred to our Endocrinology Department at King Fahd Medical City (KFMC) in 2017 for evaluation of bilateral breast enlargement and hyperprolactinemia. The bilateral breast enlargement was noticed by the family 1 year prior to presentation. It was slowly progressive but not painful, with no discharge from nipples or galactorrhea, and no skin changes over the breast area. There was no report of headache, vomiting, visual impairment symptoms, or acne. He had no history of intracranial tumor or head irradiation. The parents of the patient were second-degree cousins. The patient was the eldest child among 3 healthy siblings and was developmentally normal, with average school performance.

The examination revealed a healthy-appearing patient who was not dysmorphic, pale, or jaundiced. His height was 156 cm (90th percentile), height was 156 cm (90th percentile), and body mass index was 18.5 kg/m² (80th percentile). Lentigines were found on the membrane lining the eyes and on the sclera (Figure 1). There was hyperpigmentation of the gingiva. Bilateral diffuse breast enlargement was consistent with Tanner stage III. Also, he had neither focal breast lesion nor palpable axillary lymph nodes. Pubic Hair Tanner stage was II. The physical examination also revealed enlargement of the left testis.

The clinical laboratory findings revealed a serum prolactin level of 576 ng/mL (normal is less than 20 ng/mL) and serum estradiol...
178 pg/mL (normal is 10-50 pg/ml). However, other laboratory findings, such as complete blood count, liver function test, and kidney function test, were normal. The serum sodium and potassium levels were 136 mEq/L and 3.9 mEq/L, respectively. Lactic acid dehydrogenase, luteinizing hormone, follicle-stimulating hormone, testosterone, and dehydroepiandrosterone sulfate were in normal ranges. The beta-human chorionic gonadotropin hormone and alpha-fetoprotein serum levels showed a normal profile.

An ultrasonography evaluation of the breast revealed prominent fibro-fatty tissue bilaterally, likely a manifestation of physiological gynecomastia. However, there was no evidence of suspicious solid or cystic mass lesions. An ultrasonography evaluation of the testis revealed multiple microcalcifications (Figure 2). The computed tomography (CT) scan of the pelvis revealed bilateral testicular calcification, larger on the left side (Figure 3).
Based on findings of ultrasonography, testicular biopsy was performed, which revealed a large-cell calcifying Sertoli cell tumor (Figure 4). The case was discussed in the Tumor Board meeting and conservative treatment with regular follow-up was initiated.

High-dose adrenocorticotropic hormone (ACTH) stimulation testing revealed a normal profile and did not suggest a diagnosis of adrenal insufficiency. Similarly, molecular genetics reports on congenital adrenal hyperplasia also were negative. The low-dose (1-mg) overnight dexamethasone suppression test showed high cortisol levels, at 139 nmol/l (a normal range: 5-50 pg/mL), a paradoxical rise in serum cortisol level to 503 nmol/l, and 24-h urine free cortisol at 0.8 (normal range: 5-50 pg/mL), a paradoxical rise in serum cortisol level to 0.8 (normal range: 5-50 pg/mL), which is characteristic of primary pigmented nodular adrenocortical disease (PPNAD). Therefore, the diagnosis of ACTH-independent Cushing syndrome (CS) was confirmed. The left testicular mass biopsy report (Figure 4) described a sex cord-stromal tumor, favoring large-cell calcifying Sertoli cell tumor. Thus, because of large-cell calcifying Sertoli cell tumor of the testis and PPNAD, the diagnosis of CNC was suspected.

Molecular genetic analysis (Table 2).

Table 1. Six-day standard (2-step) dexamethasone suppression test.

<table>
<thead>
<tr>
<th></th>
<th>ACTH Pmol/l</th>
<th>Cortisol nmol/l</th>
<th>24-h urine cortisol nmol/L</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>1.4 (1.6-13.9)</td>
<td>215</td>
<td>333+ (15-224)</td>
</tr>
<tr>
<td>4th day</td>
<td>1.6</td>
<td>232</td>
<td></td>
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<tr>
<td>6th day</td>
<td>0.8</td>
<td>503</td>
<td>1000++</td>
</tr>
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ACTH – adrenocorticotropin hormone; Pmol/l – picomoles per liter; nmol/l – nanomoles per liter.

Table 3. Invasive adrenal venous sampling for cortisol, aldosterone, and adrenaline levels.

<table>
<thead>
<tr>
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<th>Right adrenal</th>
<th>Left adrenal</th>
<th>Inferior vena cava</th>
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<tbody>
<tr>
<td>Cortisol</td>
<td>3532 nmol/l</td>
<td>6290 nmol/l</td>
<td>180 nmol/l</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>960 ng/dl</td>
<td>383 ng/dl</td>
<td>8.6 ng/dl</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>5310 ng/l</td>
<td>1020 ng/l</td>
<td>80 ng/l</td>
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nmol/l – nanomoles per liter; ng/dl – nanograms per deciliter.

PRKAR1A – Protein Kinase CAMP-Dependent Type 1 Regulatory Subunit Alpha, SNP – single nucleotide polymorphism. Molecular analysis, using next-generation sequencing (NGS) panel for LCCST, identified heterozygous pathogenic variant in the PRKAR1A gene (nonsense mutation at nucleotide number 682 with change of nucleobase cytosine to thiamine, resulting of amino acid change to arginine).

A blood sample was sent to Centogene Lab (Germany), at which a gene panel for LCCSCT using next-generation sequencing (NGS) was done and showed heterozygous, nonsense mutation in the PRKAR1A gene, likely a pathogenic variant, consistent with the genetic diagnoses of Carney complex type 1.

Regarding other possible comorbidities of CNC, a wide examination was performed to exclude the involvement of other organs. Ultrasonography for the thyroid and pelvis, as well as echocardiography, did not reveal abnormalities. Brain and pituitary gland MRI were normal.

Invasive bilateral adrenal venous sampling was done (Table 3), and showed almost double the normal amount of cortisol secretion from the left adrenal gland, which confirmed the presence of left adrenal lateralization (predominance) as a source of cortisol secretion. After confirming the diagnosis, the family members were offered genetic testing for the same mutation (target gene mutation test), the mother and siblings have not carried the mutation (wild-type gene). His father was unable to undergo genetic testing because of special social circumstances. The patient underwent bilateral mastoplasty because of distressing gynecomastia. For the Cushing syndrome, the conservative management vs laparoscopic adrenalectomy was initially discussed with the family, and as the patient was not showing any apparent clinical manifestation of Cushing syndrome, conservative management was initiated.
Table 4. Diagnostic criteria of Carney complex.

<table>
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<th>Major criteria</th>
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<tr>
<td>1. Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)</td>
</tr>
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<td>2. Myxoma (cutaneous and mucosal) or cardiac myxoma</td>
</tr>
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<td>3. Breast myxomatosis or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis</td>
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<tr>
<td>4. Primary pigmented nodular adrenocortical disease or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle’s test</td>
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<td>5. Acromegaly as a result of growth hormone-producing adenoma</td>
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<tr>
<td>6. Large-cell calcifying Sertoli cell tumor or characteristic calcification on testicular ultrasound</td>
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<tr>
<td>7. Thyroid carcinoma (at any age) or multiple hypoechoic nodules on thyroid ultrasound in prepubertal child</td>
</tr>
<tr>
<td>8. Psammomatous melanotic schwannomas</td>
</tr>
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<td>9. Blue nevus, epithelioid blue nevus (multiple)</td>
</tr>
<tr>
<td>10. Breast ductal adenoma (multiple)</td>
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<tr>
<td>11. Osteochondromyxoma</td>
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<th>Supplemental criteria</th>
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<tbody>
<tr>
<td>1. Affected first-degree relative</td>
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<tr>
<td>2. Activating pathogenic variants of PRKACA (single base substitutions and copy number variation) and PRKACB</td>
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<tr>
<td>3. Inactivating mutation of the PRKAR1A gene</td>
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The patient has also manifested primary pigmented nodular adrenal disease (PPNAD), in association with ACTH-independent Cushing syndrome (CS). The diagnosis of ACTH-independent CS related to PPNAD can be challenging and the best screening test for CS is measurement of urine free cortisol excretion [18]. The current case report found more than 1000 nmol/L free cortisol in a 24-h urine sample on day 6 of the dexamethasone suppression test. Moreover, a low serum ACTH level of 0.8 (normal range: 5-50 pg/mL) and serum cortisol level of 503 nmol/L were noted. Our patient had a less aggressive course of the CNC in comparison to a previous case report by Rosenblum et al in 2017 [1], in which the patient had LCCSCT, pancreatic cancer, and Cushing syndrome due to adrenocortical carcinoma.

The patient is 16 years old at present. During regular follow-up visits in the urology clinic, he has been reporting left testicular pain, for which testicular US was repeated and showed significant progression of left testicular calcification, and a radical left orchiectomy was planned. In the endocrine clinic, he started to show intermittent elevation in blood pressure, higher BMI (29-31) kg/m², and new appearance of pink stria on the abdominal wall. His repeated Hba1c, thyroid function test, and IGF-1 levels were normal. For the Cushing features, 24-h urine collection for urinary free cortisol (UFC) excretion showed a level of 34.7 mcg/m²/day (normal level is less than 70 mcg/m²/day), with follow-up for reevaluation.

Discussion

This case report shows that gynecomastia can be the presenting feature of an underlying multisystem disorder, which mandates thorough examination and tailored investigation to reach a diagnosis. We presented a patient with classic clinical characteristics of CNC, including spotty skin pigmentation on the membrane lining the eyes and on the sclera, LCCSCT, and ACTH-independent Cushing syndrome – PPNAD. The molecular genetic analysis identified a known pathogenic mutation of PRKAR1A. Considering all this together, our patient met the diagnostic criteria of CNC (Table 4) [7]: (1) spotty skin pigmentation with the distinctive presence on the face, lip, and sclera; (2) LCCSCT, as confirmed by testicular biopsy result; and (3) ACTH-independent Cushing syndrome caused by PPNAD (as identified in our patient).
was classified as having subclinical CS. The preferred treatment option for PPNAD with overt CS is bilateral total adrenalectomy [24]. A laparoscopic approach has a lower rate of morbidity in comparison to the open technique, and it involves less postoperative pain, shorter length of hospital stay, and low overall cost [19]. In case of surgical failure or before adrenalectomy, pharmacotherapy with ketoconazole, metyrapone, mitotane, and trilostane alone or in combination can control hypercortisolism by inhibiting steroidogenesis. Fluconazole has recently been suggested as a safer alternative to ketoconazole [25].

Conclusions

We presented a case of CNC with gynecomastia, large-cell calcifying Sertoli cell tumor (LCCSCT) of the testis and primary pigmented nodular adrenocortical disease. PPNAD is a rare cause of ACTH-independent CS in childhood and can indicate underlying CNC. Moreover, LCCSCTs are very rare tumors and most of them are benign. It is highly recommended that clinical assessments and genetic tests be conducted promptly in such patients. The account of clinical manifestations of this patient adds to the knowledge about CNC and PRKAR1A mutations. The ability to distinguish CNC is important for the prevention of severe complications. PRKAR1A mutation analysis must be conducted as soon as possible in suspected CNC patients.

Declaration of Figures’ Authenticity

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References: