A case of Carney complex presenting as acute testicular pain

Adam Alleemudder, Rajiv Pillai
Department of Urology, Colchester Hospital University NHS Foundation Trust, Essex, CO4 5JL, UK

INTRODUCTION

Carney's complex is an extremely rare genetic disorder inherited by autosomal dominance or by sporadic de novo genetic defects. Over half of the cases are familial. At the last estimate there were only 750 patients worldwide with the condition. The most commonly found defect in two thirds of cases is mutation of the PRKAR1A tumor suppressor gene on Chromosome 17. It leads to a triad of manifestations namely pigmented lesions of the skin and mucosa, myxomas and multiple endocrine tumors. Although they only account for 1.5% of all testicular tumors, 40% of patients with this condition will develop large cell-calcifying Sertoli cell tumors, the majority of which have a low malignant potential.

CASE REPORT

We describe the case of a 7-year-old boy who initially presented as an emergency with acute left testicular pain and a scrotal exploration was performed. This demonstrated a normal untwisted left testis with a raised 1 cm paratesticular lesion of unknown significance lying between the posterior aspect of the testis and the body of the epididymis. As there was no evidence of torsion, a decision was made to return the testis to the scrotum and a provisional diagnosis of epididymitis was made. An ultrasound scan after 2 weeks of antibiotics showed bilateral microcalcification and a 2 mm hypoechoic lesion in the right testis in addition to the 1.4 cm left vascular paratesticular lesion. The testicular tumor markers were all normal. He was referred to a tertiary care center where excision of the left-sided lesion and excisional biopsy of the right lesion confirmed benign bilaterally Sertoli cell tumors. Closer physical examination later found precocious puberty and spotty freckles which raised suspicion that led to genetic testing and the subsequent diagnosis of Carney's complex (CNC).
DISCUSSION

CNC is a rare genetic syndrome, first described in 1985, comprising pigmented skin and mucosal lesions, myxomas, and multiple mainly endocrine neoplasms. The majority arise from autosomal dominant inheritance with a smaller number from sporadic de novo mutations. There are at least 750 patients known with the disease from a variety of ethnic backgrounds with women affected in two-thirds of cases.

The most common genetic defect in over 70% is mutation of the PRKAR1A tumor suppressor gene located at 17q22-24 which encodes for the type 1α subunit of protein kinase A involved in the cAMP signaling pathway. Another mutation, which clinically manifests later in life, is found at the 2p16 region although the exact nature and function of this gene(s) is unknown.

CNC is characterized by a varied list of manifestations and diagnosis is usually made in the second decade based on certain criteria [Table 1]. Once suspected, genetic testing for the affected gene is warranted using sequence or deletion/duplication analysis. The most common are cutaneous lentigines that develop around puberty on the face, genitals, mucosae and lips, and cardiac myxomas which are the principle cause of mortality in 50% through restriction of blood flow or

Table 1: Clinical features and diagnostic criteria of Carney’s complex. There must be two of the major criteria confirmed by histology, imaging or biochemical testing or one major and one supplemental criteria

| Major criteria                                      | Supplemental criteria                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| Spotty skin pigmentation                            | Affected first-degree relative                                                       |
| Myxomatosis                                          | Activating pathogenic variants of PRKACA                                               |
| Primary pigmented nodular adrenocortical disease     | Inactivating mutation of the PRKAR1A gene                                              |
| Acromegaly                                          | Features suggestive of CNC, but not diagnostic                                        |
| LCCSCT                                              | Intense freckling                                                                     |
| Thyroid carcinoma or nodules                         | Blue nevus (common type)                                                              |
| Psammomatous melanotic schwannomas                  | Cafe-au-lait spots or other birthmarks                                                |
| Epitheloid Blue nevus                               | Elevated IGF-I levels, abnormal glucose tolerance test, or paradoxical growth hormone response to thyrotropin-releasing hormone |
| Breast ductal adenoma                               | Cardiomyopathy                                                                        |
| Osteochondromyxoma                                  | History of Cushing’s syndrome, acromegaly or sudden death in extended family           |

| Table 1: Clinical features and diagnostic criteria of Carney’s complex. There must be two of the major criteria confirmed by histology, imaging or biochemical testing or one major and one supplemental criteria |

| Major criteria                                      | Supplemental criteria                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| Spotty skin pigmentation                            | Affected first-degree relative                                                       |
| Myxomatosis                                          | Activating pathogenic variants of PRKACA                                               |
| Primary pigmented nodular adrenocortical disease     | Inactivating mutation of the PRKAR1A gene                                              |
| Acromegaly                                          | Features suggestive of CNC, but not diagnostic                                        |
| LCCSCT                                              | Intense freckling                                                                     |
| Thyroid carcinoma or nodules                         | Blue nevus (common type)                                                              |
| Psammomatous melanotic schwannomas                  | Cafe-au-lait spots or other birthmarks                                                |
| Epitheloid Blue nevus                               | Elevated IGF-I levels, abnormal glucose tolerance test, or paradoxical growth hormone response to thyrotropin-releasing hormone |
| Breast ductal adenoma                               | Cardiomyopathy                                                                        |
| Osteochondromyxoma                                  | History of Cushing’s syndrome, acromegaly or sudden death in extended family           |
| | Family history of carcinoma, in particular of the thyroid, colon, pancreas and ovary; other multiple benign or malignant tumors |
generation of emboli. The most common endocrine neoplasm is primary pigmented nodular adrenocortical disease where the raised cortisol leads to Cushing’s syndrome.

Testicular tumors affect 50% of patients, and the majority are large-cell calcifying Sertoli cell tumors (LCCSCT) with low malignant potential.[3] Other tumors of Sertoli cell origin include sclerosing, sex cord with annular tubules, and unspecified. Leydig cell tumors and adrenocortical rest tumors are rare. Sertoli cells play a role in structural support, in the differentiation of spermatocytes and secretion of anti-Mullerian hormone during early fetal life causing regression of the Mullerian ducts. LCCSCTs account for 1.5% of all testicular tumors and 40% occur as part of genetic syndromes.[4] The pathological production of aromatase leads to the peripheral conversion of testosterone to estradiol that causes gynecomastia and epiphyseal plate closure in long bones. It also causes precocious puberty through conversion of androstenedione to estrone which leads to increased androgen production. The tumors are often multicentric, bilateral, and contain microcalcifications in the shape of a Christmas tree pattern.[5] They tend to be asymptomatic unless macrocalcifications are present causing an overall increase in testicular size, which may obstruct the seminiferous tubules leading to infertility.

The management of CNC involves medical or surgical intervention for each specific complication or tumor; LCCSCTs causing precocious puberty, gynecomastia, or premature epiphyseal fusion usually requires medical therapy with aromatase inhibitors and/or surgery. The majority of LCCSCTs is benign though and can be managed conservatively with surveillance. Malignant LCCSCTs are found in 17% and are more common in older patients, especially when there is unilateral or unifocal disease, a large mitotic count, size larger than 4 cm or significant nuclear atypia.[4] CNC requires annual surveillance due to the high mortality and morbidity which includes echocardiography, hormonal assays for growth hormone, prolactin and insulin-like growth factor-I, pituitary magnetic resonance imaging, and ultrasound of the testis.

CONCLUSION
This unusual case highlights the importance of following up cases initially suspected as epididymo-orchitis. An awareness of CNC in urology is important due to the risks of developing testicular tumors and infertility.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VL. The complex of myxomas, spotty pigmentation, and endocrine overactivity. Medicine (Baltimore) 1985;64:270-83.
2. Correa R, Salpea P, Stratakis CA. Carney complex: An update. Eur J Endocrinol 2015;173:M85-97.
3. Wilkes D, McDermott DA, Basson CT. Clinical phenotypes and molecular genetic mechanisms of Carney complex. Lancet Oncol 2005;6:501-8.
4. Halat SK, Ponsky LE, MacLennan GT. Large cell calcifying Sertoli cell tumor of testis. J Urol 2007;177:2338.
5. Premkumar A, Stratakis CA, Shawker TH, Papanicolaou DA, Chrousos GP. Testicular ultrasound in Carney complex: Report of three cases. J Clin Ultrasound 1997;25:211-4.