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A 37-Year-Old Man with Multifocal Bilateral Malignant Testicular Large-Cell Calcifying Sertoli Cell Tumors Presenting as Painless Testicular Masses

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 37-year-old
Final Diagnosis: Large cell calcifying sertoli cell tumor
Symptoms: Testicular mass
Clinical Procedure: —
Specialty: Urology

Objective: Unusual clinical course

Background: Large-cell calcifying Sertoli cell tumor (LCCSCT) belongs to the category of sex cord stromal tumors and is extremely rare. Testicular LCCSCTs show benign or malignant behavior, appear sporadically, or are associated with genetic syndromes. Benign LCCSCTs are more commonly bilateral and multifocal and present in younger patients. The prognosis is poor when patients have advanced or metastatic disease. However, due to its rarity, the literature provides only weak evidence concerning their clinical course and treatment options. This report describes a 37-year-old man suffering from a multifocal, bilateral malignant testicular LCCSCT presenting as painless testicular masses.

Case Report: A 37-year-old man presented with bilateral painless testicular masses. Imagery showed bilateral macro-orchitis with multifocal intratesticular hyperechoic and hypointense lesions. He underwent testis-sparing surgery with the enucleation of 1 testicular lesion. The anatomopathological analysis revealed an LCCSCT whose histological characteristics indicated a benign tumor. A simple follow-up was therefore recommended. Six years after diagnosis, the patient developed lymph node metastases, and radical bilateral orchiectomy and radical lymphadenectomy were performed. A few months later, pleural, pulmonary, and bone metastases occurred. Chemotherapy and immunotherapy did not control the disease. The patient died 7 years after the initial diagnosis.

Conclusions: This case highlights the importance of the histopathology diagnosis in cases of testicular masses, and that sporadic, multifocal, and bilateral LCCSCTs present in younger men can be malignant despite the benign characteristics of the primary tumor.

Keywords: Orchiectomy • Sertoli Cell Tumor • Testicular Neoplasms • Testis • Testicular Diseases

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Introduction

Testicular tumefaction is a common concern in urology. Most causes can be easily identified through anamnesis, clinical examination, blood tests, or ultrasonography [1]. However, for testicular masses, differential diagnosis can be challenging. The 2022 WHO classification of tumors of the urinary system and the male genital organs lists 43 different types of testicular tumors, of which 8 are categorized as having unspecified, borderline, or uncertain behavior [2]. Given that testicular cancers primarily affect young males, accurate diagnosis and assessment of pathological progression are crucial for determining the most appropriate therapeutic strategy [1]. However, data on the management of many types of testicular tumors are scarce, and existing case studies are often only partially comparable. Consequently, it can be difficult to choose between a more radical treatment option and favoring the conservation of fertility and endocrine function, especially face-to-face to a young patient.

In this clinical case, we share our experience with a 37-year-old patient with a multifocal, bilateral testicular LCCSCT presenting as painless testicular masses that took an unexpected course, resulting in a fatal outcome.

Case Report

A 37-year-old man was referred to our institution in December 2015. He noticed bilateral painless testicular masses. Physical examination revealed no gynecomastia or skin anomalies. Ultrasound showed bilateral macro-orchitis with multiple intratesticular hyperechoic lesions with acoustic shadowing (**Figure 1**). These lesions were 2.4 cm and 2.1 cm on the left and right testicles, respectively. A pelvic MRI was performed, showing bilateral intratesticular lesions with clear hypointense T1 and T2 signals, which take intense contrast enhancement after gadolinium injection (**Figure 1**). The MRI revealed 10 lesions on the left testicle and 5 lesions on the right. Serum alpha-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG), lactate dehydrogenase (LDH), testosterone, estradiol, and gonadotropin levels were in normal range. A surgical testicular exploration was performed, and a right testicular nodule was enucleated and sent to a pathologist for examination. Histology revealed a benign large-cell calcifying Sertoli cell tumor with a size less than 5 cm, and the absence of mitosis, cytological atypia, vascular permeation, and necrosis (**Figure 2**). Immunohistochemistry staining was positive for vimentin, calretinin, inhibin, and cytokeratin AE1/AE3. Due to the benign histological characteristics of the testicular lesion, the decision was made not to proceed with radical orchiectomy; instead, regular follow-up was initiated. Testicular examination and testicular sonography were performed every 6 months for 2 years and then once a year. Additionally, the patient was followed up in the genetic consultation. No specific genetic testing was performed due to the absence of suggestive symptoms or a relevant family history. Endocrine testing confirmed a normal glucose profile and excluded thyroid dysfunction, pheochromocytoma, and adrenal insufficiency.

In June 2021, testicular examination revealed an induration of the left testicle. A pelvic MRI confirmed tumor infiltration

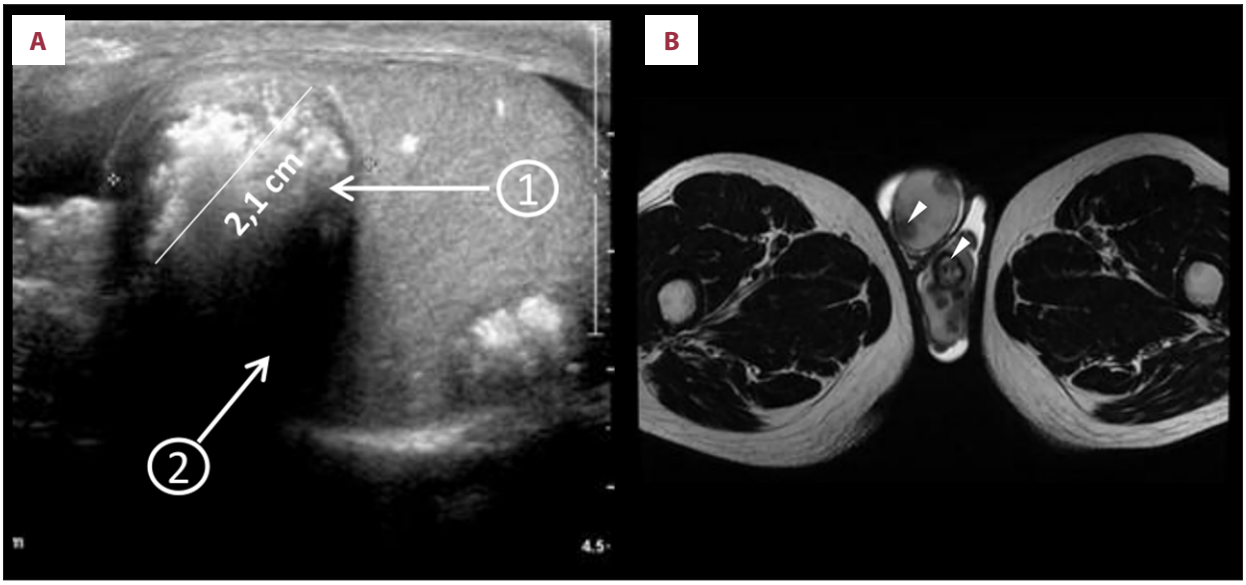

Figure 1. Imaging from testicular masses in a 37-year-old man with multifocal, bilateral, malignant large-cell calcifying Sertoli cell tumors (LCCSCTs). (**A**) Testicular ultrasound showing intratesticular hyperechoic lesions (1) with acoustic shadowing (2). (**B**) Pelvic MRI with bilateral, multifocal, intratesticular lesions (white arrows) and a clear hypointense T2 signal.

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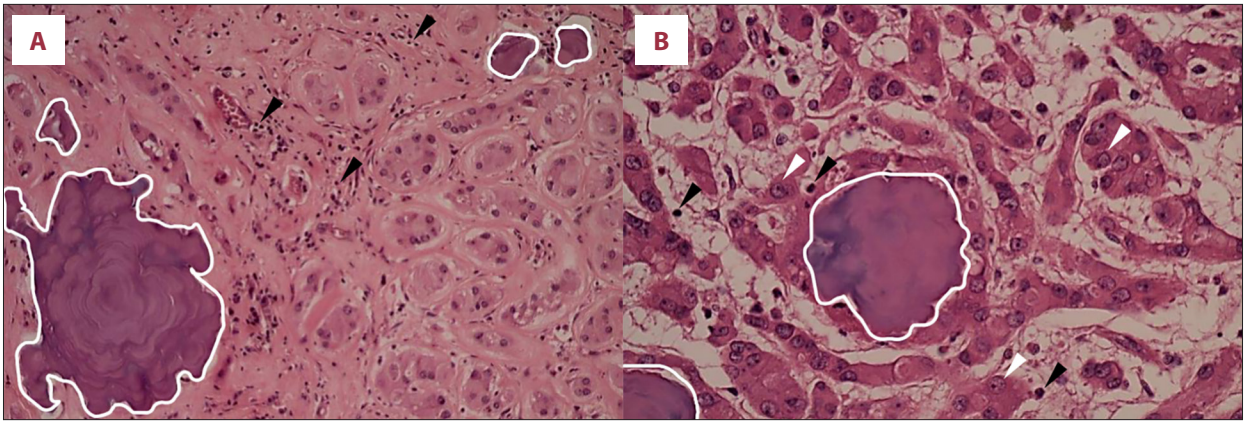

Figure 2. Photomicrographs of the diagnostic histopathology from a testicular mass in a 37-year-old man with multifocal, bilateral, malignant, large-cell calcifying Sertoli cell tumors (LCCSCTs). (**A, B**) Histological representation of testicular sections with disorganized tissue architecture, containing laminated Psammomatous mulberry-like calcifications (purple, white delineation, **A, B**) with inflammatory infiltration (black arrows, **A, B**), and replacement of the normal testicular tissue with large epithelioid cells including eosinophilic cytoplasm and prominent nucleoli (white arrows, **B**) with minimal cytological atypia. Hematoxylin and eosin (H&E). Magnification 20× (**A**) and 40× (**B**).

at the upper pole of the testicle with infiltration of the spermatic cord. The patient underwent left radical orchiectomy. Anatomopathological analysis demonstrated a multifocal large-cell calcifying Sertoli cell tumor (the largest lesion was 6.5 cm) with invasion of the spermatic cord and many neoplastic vascular permeations. A thoracoabdominal CT scan revealed left para-aortic lymphadenopathy, multiple pulmonary nodules, and osteo-condensing lesions of the spine. A PET scan was performed and showed a nodular formation at the base of the penis, several moderately hypermetabolic lymph nodes in the left inguinal and left external iliac regions, and large hypermetabolic lymph nodes extending from the left renal vein to the aortic bifurcation. There was no hypermetabolic lesion in the lungs. The patient underwent a lumbo-aortic and iliac lymph node dissection, as well as right radical orchiectomy. Histology showed metastatic invasion of the lumbo-aortic and iliac lymph nodes with capsular effraction. The right testicle presented a multifocal large-cell calcifying Sertoli cell tumor. In November 2021, the patient developed a local extension with invasion of the penis and the left inguinal canal. Furthermore, supra- and sub-diaphragmatic lymphadenopathy as well as pleural, pulmonary and bone metastases appeared. In December 2022, chemotherapy (vinblastine, cisplatin, and ifosfamide) was initiated, but after only 2 cycles, the cancer continued to progress. Therapy was switched to paclitaxel (5 cycles), but the disease continued to evolve rapidly. The patient entered a clinical trial testing Axitinib and pazopanib, but ultimately died 7 months later in palliative care.

Discussion

Here, we described a rare case of a young patient presenting a multifocal, bilateral testicular LCCSCT with benign histological characteristics. A testis-sparing approach was followed before the pathology started to show malignant behavior and ultimately caused the death of the patient. Our case highlights the importance of knowing all the types of Sertoli cell tumors and the associated risk for malignant behavior to make the right diagnosis and choose the most appropriate therapeutic management.

About 95% of primary testicular tumors develop from germs cells and only <5% arise from sex cord stromal cells [3-5]. According to the WHO classification, sex cord stromal tumors (SCSTs) account for 4% of testicular tumors and are classified as Leydig, Sertoli, granulosa, mixed, and unclassified cell tumors [4]. Leydig cell tumors are the most common, representing over 90% of SCSTs [6]. Sertoli cell tumors are a very rare type of testicular neoplasm, accounting for 0.1-1.5% of all testicular tumors [6-8]. They commonly present as testicular masses and can be associated with signs of increased estrogen activity, most often gynecomastia [6]. Most Sertoli cell tumors, such as sclerosing Sertoli cell tumors, are classified as “not otherwise specified” (NOS). LCCSCT and intratubular large-cell hyalinizing Sertoli cell tumors are recognized as 2 histologically distinct types of Sertoli cell tumors [4,8]. Large-cell calcifying tumors are commonly seen in young patients, with an average age at diagnosis of 21 years [6]. It can affect 1 or both testicles in a multifocal manner. Frequently, these tumors are associated with extragonadal endocrine signs and symptoms (gynecomastia, precocious puberty, acromegaly, feminization, or, rarely, virilization) or with complex syndromes (Carney complex (10-40% of LCCSCTs) or Peutz-Jeghers syndrome) [9-11]. Scrotal ultrasound has a high sensitivity to diagnose testicular tumors [12]. LCCSCT appear as an intratesticular hyperechoic lesion (large areas of dense curvilinear calcifications) with

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acoustic shadowing and increased vascularity [13]. Due to artifacts caused by prominent calcifications, it can be hard to evaluate the internal vasculature of the lesions. An MRI may also be conducted to further specify the lesions, although it is not indispensable. Computed tomography (CT) of the pelvis, abdomen, and chest serves for staging of metastatic disease after histological confirmation of LCCSCT. Typical tumor markers such as LDH, AFP, and β-hCG are typically not elevated in SCST, but indicate germ cell tumors. In contrast, hormonal markers such as testosterone, luteinizing hormone, and follicle-stimulating hormone are commonly elevated in SCST [12].

Histology and immunohistochemistry are the only ways to assure a definitive diagnosis. LCCSCTs are characterized by large eosinophilic cells presenting nodular or sheet-like growth and intratubular proliferation. These are associated with laminated psammomatous, mulberry-like, and/or dystrophic calcifications, a prominent neutrophilic infiltrate, and a lymphocytic rim. Significant cytologic atypia may be present [4,14]. Immunohistochemistry highlights the expression of vimentin, calretinin, inhibin, and cytokeratin [12]. Nuclear localization of ß-catenin appears to be common in Sertoli cell tumors, with the exception of LCCSCTs, which are typically negative. This might prove useful for differential diagnosis [15]. The pathologist should differentiate between benign and malignant Sertoli cell tumors and determine the risk factors for metastatic disease. This allows the urologist to choose the best treatment option and also determines when staging, follow-up, or adjuvant therapy are recommended. According to the World Health Organization classification, the risk factors for malignant disease are: tumor size > 5 cm, invasive growth pattern, necrosis, and cellular pleomorphism [4]. The recent systematic review and meta-analysis of Grogg et al identified additional potential risk factors for metastatic disease: high mitotic index and extension to the spermatic cord. Moreover, they suggest lowering the cut-off for tumor size to >2.4 cm [16]. In the case of LCCSCTs, malignancy appears to be linked to sporadic cases and is rare in genetic syndromes, in which LCCSCTs exhibit benign behavior [11]. Molecular analyses can help further identify primary tumors with malignant potential that express multiple pathogenic variants of the PRKAR1A gene [11].

With approximately 10% of SCSTs and 15% of LCCSCTs being cancerous, most of these tumors have a favorable prognosis and rarely metastasize to lymph nodes or other visceral sites [6,14]. However, the prognosis is poor when patients have advanced or metastatic disease [17]. Managing the primary tumor is challenging. No prospective comparative data are available between testis-sparing surgery (TSS) and radical orchiectomy. However, some case series showed that TSS can be a treatment option because it is not thought to be associated with an increased risk of recurrence or metastatic disease. Essentially, TSS should be reserved for small tumors with 0 to 1 risk factors [16,17]. This was confirmed by a recent study presenting a case of bilateral benign LCCSCTs in a young male with Carney complex who underwent a testis-sparing approach, which further highlights the importance of a holistic approach that considers clinical, radiological, and histopathological features [18].

Data on the management of advanced pathology (≥IIA, pT/X, N1, M0, S0/1) are very scarce. Retroperitoneal lymph node dissection (RPLND) in the case of enlarged retroperitoneal nodes is the most promising approach. It showed success with improvement of disease-free survival, with a preference of immediate over delayed RPLND [17]. In case of oligometastatic disease, resection of all metastatic sites should be considered whenever possible [16]. Unfortunately, systemic chemotherapy and radiation therapy have low response rates and are reserved for palliative therapy [16,17].

Conclusions

LCCSCTs are very rare tumors. Most of them are benign and have a favorable prognosis. Testis-sparing surgery may be an option in case of small tumors with zero to 1 histological risk factors, but the potential malignity of the tumor should be kept in mind. Patients with nodal metastases may benefit from retroperitoneal lymph node dissection. Systemic chemotherapy and radiation therapy did not prove effective in our patient.

This case highlights the importance of histopathology diagnosis in cases of testicular masses, and that sporadic, multifocal, and bilateral LCCSCTs present in younger men can be malignant despite the benign characteristics of the primary tumor.

For our patient, a bilateral radical orchiectomy should have been the initial treatment of choice.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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