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Case Report
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Leydig Cell Tumor of the Testis, Presenting with Hypogonadism and Azoospermia

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Abstract

Leydig Cell Tumors (LCTs) are rare neoplasms that account for only 5% of all testicular cancers. Although frequently asymptomatic, LCTs commonly present as precocious puberty in young children or endocrine abnormalities in adults between 30 and 60 years old. Endocrine changes are related to the hormonally active nature of Leydig cells, which are responsible for producing androgens. Standard treatment for LCTs is a radical orchiectomy, and after resection, LCTs are diagnosed through histopathological identification of their characteristic eosinophilic cytoplasm and Reinke crystal inclusion bodies. We report an atypical case of a benign LCT in a 26-year-old man with azoospermia and hypogonadism.

Introduction

Testicular cancer is a relatively rare cancer that accounts for only 1.0% to 1.5% of all neoplasms in men. There are two types of Testicular Cancers: Germ Cell Tumors (GCTs), the most common, constitute 95% of all cases, and Sex Cord-Stromal Tumors (SCSTs), which account for only 5% of Testicular Cancers. Leydig and Sertoli cells, which are vital for androgen production and spermatogenesis, are the two cell populations in SCSTs. Leydig Cells Tumors (LCTs) are the most common SCST, accounting for 1% of all testicular cancers. Unlike GCTs, which are often malignant, LCTs are generally benign, and malignant in only 10% of adults. There are no known risk factors for developing LCTs, including cryptorchidism, which is commonly associated with the development of GCTs. Unlike GCTs, tumor markers Alpha-Fetoprotein (AFP), Human Chorionic Gonadotropin (HCG) Lactate Dehydrogenase (LDH), are within normal limits for adults with LCTs [1].

Although LCTs can occur at any age, the incidence has a bimodal distribution, with peaks in prepubescent children and men between 30 and 60 [2]. The clinical presentation of men with LCTs is variable, ranging from completely asymptomatic to painfully enlarged testicles. Children normally present with precocious puberty if the Leydig cells are hormonally active. Adults may present with endocrine dysfunction in 20% to 30% of cases [1]. Most commonly, this dysfunction manifests as gynecomastia, but infertility and impotence are also possible. Excessive sex hormone secretion from LCTs can disrupt the Hypothalamus-Pituitary-Adrenal (HPA) axis, altering the levels of Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), testosterone, and other hormones [3].

Standard treatment for all suspected testicular neoplasms is radical orchiectomy. After resection, a histopathological diagnosis is made, and LCTs are identified by their granular, eosinophilic cytoplasm and characteristic Reinke crystals inclusion bodies [4]. Prognosis for patients diagnosed with early stage LCTs is favorable, with one- and five-year survival rates at 98% and 91% respectively.

In this article, we describe an atypical presentation of a LCT in a male with hypogonadism and azoospermia.

Case Presentation

In the summer of 2018, a 26-year-old Caucasian male presented to an emergency room with back pain radiating down the right leg after a fall. The patient also endorsed right testicular pain, despite no apparent trauma to the region after falling. Initial work-up included a Complete Blood Count (CBC), chest x-ray, and Ultrasound (US) of the right testicle. The CBC revealed a slightly elevated white blood cell count of 11.93 K/uL (normal range 0 K/uL to 10 K/uL) with a differential significant for eosinophilia (8.8%, normal range 0% to 6%). The chest x-ray was normal. The US demonstrated an ovoid, heterogeneous, solid 4.0 cm × 2.4 cm × 3.0 cm mass with internal vascularity. The patient was referred to medical oncology and urology evaluation of suspected testicular cancer.

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Table 1: Hormonal levels before and after surgery.

	16-Jul	25-Jul (Date of Surgery)	31-Jul
Testosterone	307	154	10
Estradiol	-	71	<10
LH	-	0.1	0.5
FSH	-	0.1	2.9
Prolactin	-	29	6

The patient is 177.8 cm tall, weighs 67.8 kilograms, and has a BMI 53.06. The physical exam was unremarkable, with the exception of a palpable mass in the right testicle but no evidence of gynecomastia or inguinal lymphadenopathy. A dipstick urinalysis revealed microscopic hematuria. The patient endorsed intermittent pain in his right testis for the past 12-months, but did not seek medical evaluation. His past medical history is significant for a 12-pack year tobacco smoking history and uncontrolled hypertension (160/114 mm Hg). There is a history of breast cancer, multiple myeloma, and thymus cancer in the mother, father, and brother respectively. He also reports a history of testicular cancer in his paternal uncle. He reports normal timing and sequence of puberty, normal libido and sexual ability, and denies any history of cryptorchidism. Six months prior to presentation, the patient and his partner had been unsuccessful in their attempts to get pregnant.

Preoperative laboratory analysis of serum tumor markers AFP, HCG, and LDH were all within normal limits. A preoperative hormonal panel was markedly abnormal, with nearly undetectable levels of FSH and LH, elevated prolactin and estradiol, and levels of testosterone within the range of hypogonadism (Table 1). Two semen analyses conducted in-hospital two days apart revealed azoospermia. A preoperative CT scan of the abdomen and pelvis showed no evidence of metastatic disease but revealed a malrotated right kidney and minimal umbilical and inguinal hernias. The patient underwent a right radical orchiectomy. Pathological examination of the resected mass revealed a benign 3.6 cm Leydig Cell Tumor (pT1bNx) local to the testis with no evidence of necrosis, lymphovascular or spermatic cord invasion. A post-operative endocrine panel was conducted immediately after the operation and one week later (Table 1).

Discussion and Conclusion

LCTs are uncommon tumors that account for 1% to 3% of all testicular cancers. These tumors typically occur in young children and adults between the ages of 30 and 60. LCTs are always benign in children, while 10% of cases in adults are malignant. When hormonally active, the tumors often produce androgens, mainly testosterone and estrogen. While LCTs are frequently asymptomatic, endocrine dysfunction often causes patients to seek medical evaluation. In children, dysfunction manifests as precocious puberty due to excessive testosterone production from the Leydig cells. High levels of testosterone lead to premature activation of the HPA axis causing early genital development, facial hair growth, and deepening voice. In adults, excessive androgen levels can cause gynecomastia, loss of libido, or impotence [1].

Although LCTs are most commonly benign, radical orchiectomy is the mainstay therapy for all suspected testicular cancers because the majority of testicular masses are malignant [5]. Diagnosis of LCTs is made after surgical resection through a histopathological identification of an eosinophilic granular cytoplasm with Reinke crystal inclusion bodies.

In this case, our patient presented with a painful testicular mass prompting US examination. At 26 years old, he is outside of the two age groups with the highest incidence. Consistent with previous case series, all serum tumor markers were negative. The mass was unilateral and benign, which is seen in 90% of LCTs. At presentation, the patient was severely obese (BMI=53.06). There was no evidence of gynecomastia or erectile dysfunction. However, the patient presented with suspected infertility after months of trying to get his partner pregnant. A hormonal profile prior to surgery revealed HPA axis suppression and hypogonadism. Separate semen analyses revealed azoospermia. In previous cases, the proposed mechanism underlying LCTs associated with azoospermia involved excessive testosterone production from the Leydig cells, leading to LH suppression and impaired spermatogenesis [6]. However, in our case, the patient presented with a testosterone of 307 ng/ml level significantly lower than normal for adult males and not nearly high enough to cause feedback inhibition on LH release. Moreover, hypogonadism in men with LCTs is rare, as Leydig cells are principally responsible for secreting testosterone. An endocrine profile taken immediately post-operatively revealed abnormally high levels of estrogen and prolactin, decreased levels of testosterone from baseline, and marked suppression of FSH and LH. At one-week post-operation, the testosterone decreased level 10 ng/ml, while the estrogen and prolactin levels returned to normal. Although outside of the normal range, LH and FSH levels were increased from baseline, suggesting that elevated estrogen levels inhibited FSH and LH release.

The mechanism behind the azoospermia in our patient is unclear. He is significantly obese, and there is a well-established relationship between low testosterone and obesity [7]. Also, in adipose tissue, aromatase and aldo-keto reductase metabolize testosterone into estrogen, possibly explaining the elevated levels in our patient [8]. Estrogen has both a direct and indirect stimulatory effect on the release of prolactin, which could lead to elevated levels of prolactin in this case [9]. In males, hyperprolactinemia is associated with erectile dysfunction and infertility [10]. Hypogonadism, combined with the hyperprolactinemia, could have contributed to the azoospermia in our patient. However, the estrogen and prolactin levels were only mildly elevated, and other than infertility, our patient did not endorse any of the other common symptoms associated with hypogonadism or hyperprolactinemia, including decreased libido, impotence or gynecomastia [11]. An alternative explanation for the hypogonadism and infertility in our patient could involve the role of Sex Hormone Binding Globulin (SHBG). Higher levels of SHBG are associated with lower levels of testosterone, which could cause hypogonadism. However, obesity is strongly associated with lower levels of SHBG, and an elevated level in our severely obese patient is unlikely [12].

This patient has been loss to follow-up since one-week post operation. This has prevented further exploration of the levels of SHBG and changes to his levels of testosterone, LH, FSH, and estradiol. Additionally, examining the possible reversibility of the azoospermia would only be possible three months after the operation to allow adequate time for spermatogenesis. Several previous case studies have reported reversible infertility after orchiectomy in males with LCTs [5,13,14]. However, the unusual finding of hypogonadism in the setting of a patient with a hormonally active LCT makes this unlikely.

In conclusion, we present an atypical case of a male with a benign LCT of the testis. LCTs are very rare testicular cancers that have a variable clinical presentation. If symptomatic, LCTs may

cause elevated testosterone levels, gynecomastia and impotence. Our patient presented with hypogonadism and azoospermia. With the exception of the testosterone, the endocrine abnormalities in our patient partially resolved after surgery, however a complete analysis was not possible without the patient reestablishing care.

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