

Leydig cell tumors are rare testicular tumors of the male gonadal interstitium. Although uncommon, Leydig cell testicular neoplasms are the most common sex cord-stromal tumors and comprise 1–3% of all testicular neoplasms. This tumor is always benign in children and approximately 90% are benign in adults. In most cases, patients present with an incidental finding of a testicular mass on scrotal ultrasonography during evaluation of hydroceles or varicoceles or during diagnostic workup for infertility. Leydig cell tumors have been primarily managed with radical inguinal orchiectomy. However, conservative management with testis-sparing surgery in younger adults and children were reported in the literature. Here we report a case of bilateral Leydig cell tumor of the testis treated with radical orchiectomy who presented with the complaint of infertility and no disease recurrence in followup for 9 months. The patient is currently disease-free and under androgen supplementation for androgen insufficiency. We recommend complete exam and diagnostic workup in patients with infertility and azoospermia.

Key words: Leydig cell tumors, testis, infertility, orchiectomy.

Bilateral Leydig cell tumor of the testis: a case report

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Introduction

Leydig cell tumors are rare testicular tumors of the male gonadal interstitium. Although uncommon, Leydig cell testicular neoplasms are the most common sex cord-stromal tumors and comprise 1–3% of all testicular neoplasms [1]. The majority have been recognized in males between the ages of 20 and 60 years. However, approximately one fourth have been reported before puberty [2]. They are frequently hormonally active, leading to feminizing or virilizing syndromes. Approximately 10% of Leydig cell tumors are bilateral and 10% are malignant. The malignant variants occur only in adults and metastasis is the major criterion of malignancy [3]. Malignancy has not been reported in Leydig cell tumors in children. The etiology of Leydig cell tumors remains unknown. It is thought that an endocrine role may contribute to the development of these tumors. They have a tendency to cause endocrine manifestations, and testicular swelling, decreased libido (20%) and gynecomastia (15%) are common symptoms in adults [4, 5]. Leydig cell tumors were once managed primarily with radical orchiectomy [6–8]. However, testis sparing surgery has been used increasingly in both the adult and pediatric populations. Here we report a new case with bilateral testicular Leydig cell tumor in order to review the clinical, diagnostic and therapeutic aspects of this uncommon tumor.

Case report

A 30-year-old patient presented with a complaint of infertility since two years of marriage. Spermatogram showed oligoasthenoteratospermia. Physical examination of the external genitalia revealed atrophic left testis and no palpable tumor mass and a solid painless mass in the upper right testicular pole in the patient. Bilateral testicular tumor was shown by scrotal Doppler ultrasound examination, which originated from the bilateral mediastinum testis. There was no gynecomastia. Hormonal assay showed normal plasma levels of α -fetoprotein (AFP), β -human chorionic gonadotropin (HCG), lactate dehydrogenase (LDH), estradiol, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and serum testosterone. Urinary 17-ketosteroids were not measured. Chest X ray and abdomen CT scan showed no evidence of metastatic spread. Sperm cryopreservation was done before the surgical procedure. The patient underwent bilateral radical orchiectomy; because both tumors originated from the mediastinum testis, testis sparing surgery was not performed. A frozen section during surgery from the bilateral testis was suggestive for Leydig cell tumor which was confirmed by histopathological examination showing bilateral Leydig cell tumor of the testis. The gross examination of the right testis showed a well-circumscribed, brown homogeneous solid mass with soft consistency measuring 2.5 cm in diameter. The microscopic examination revealed a nodular pattern of large polygonal cells with round nuclei and eosinophilic cytoplasm (Fig. 1). Necrosis was not seen. The mitotic count was very low. Tunica albuginea and spermatic cord involvement

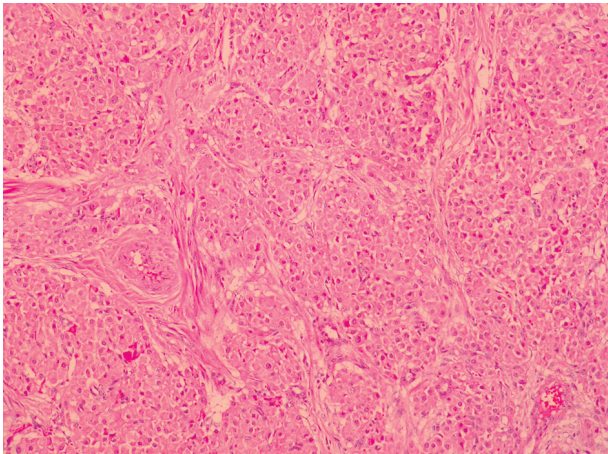


Fig. 1. Histological section of Leydig cell tumor in the right testis. The tumor cells have abundant eosinophilic cytoplasm and round nuclei. H&E, 200×

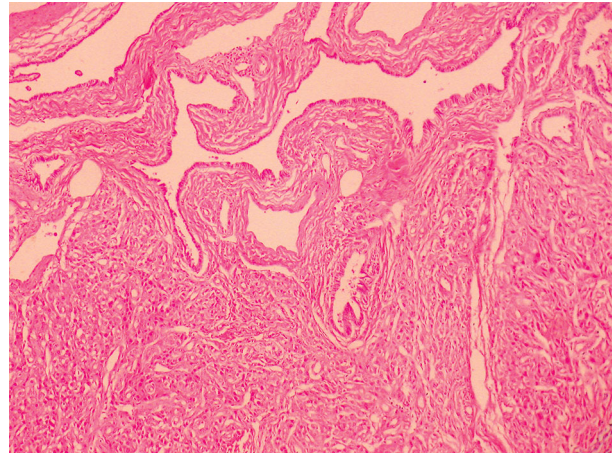


Fig. 2. Rete testis involvement, H&E, 100×

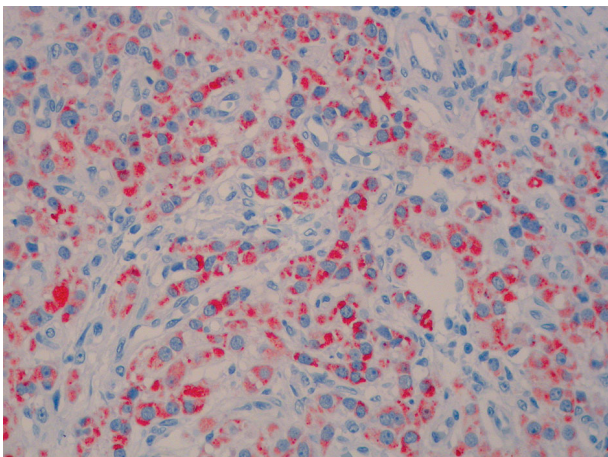


Fig. 3. Melan-A immunoreactivity in tumor cells, 200×

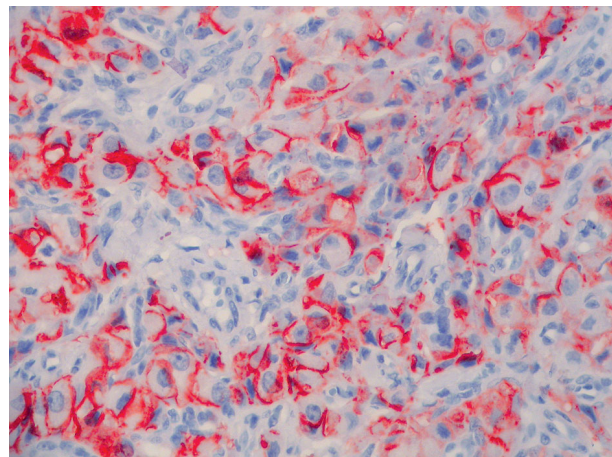


Fig. 4. CD 56 immunoreactivity in tumor cells, 100×

were not seen; however, rete testis involvement was identified (Fig. 2). Immunohistochemically, the tumor cells were positive for inhibin- α , melan-A and CD56, but negative for ACTH and p53 (Fig. 3).

The tumor in the left testis was 2.5 cm in diameter. Histopathological features of the left testicular tumor were similar to the tumor in the right testis. Microscopically similar histological features were seen in the left testicular mass.

There was no disease recurrence in follow-up for 9 months and the patient is currently disease-free and under androgen supplementation for androgen insufficiency.

Discussion

The etiology of Leydig cell tumors remains unknown. Unlike germ cell testicular tumors, Leydig cell neoplasms are not associated with cryptorchidism. An endocrine function may contribute to the development of these tumors. For example, excessive stimulation of Leydig cells with luteinizing hormone due to a disorder of the hypothalamic-pituitary axis may induce their oncogenesis. Animal models have also demonstrated Leydig cell tumorigenesis following long-term

estrogen administration. Although these tumors usually secrete testosterone, the production of estrogen, progesterone, and corticosteroids has also been shown. Estrogen excess and feminizing syndromes may occur from the peripheral aromatization of testosterone or from the direct production of oestradiol by the tumor itself. In 20% of the cases, increased oestradiol and decreased testosterone levels result in feminization in the adult and masculinization in the child. The endocrinological manifestations may precede the palpable testicular mass, which is the most common presenting feature. Suardi *et al.* presented the largest case study of Leydig cell tumor and 32% of the patients referred for a testicular mass, 8% for gynecomastia, 8% for testicular pain, 11% for infertility and 5% for isosexual pseudo-puberty [8]. Carmignani *et al.* presented 24 cases with one bilateral tumor. Testicular tumor markers (β -HCG, LDH, AFP) were negative in all patients and one patient with gynecomastia showed high preoperative testosterone levels [9]. In our case no hormonal abnormality was present, serum tumor markers were in the normal range, and palpable testicular mass was the only manifestation of the tumor. In pure Leydig cell tumors, levels of serum tumor markers such as

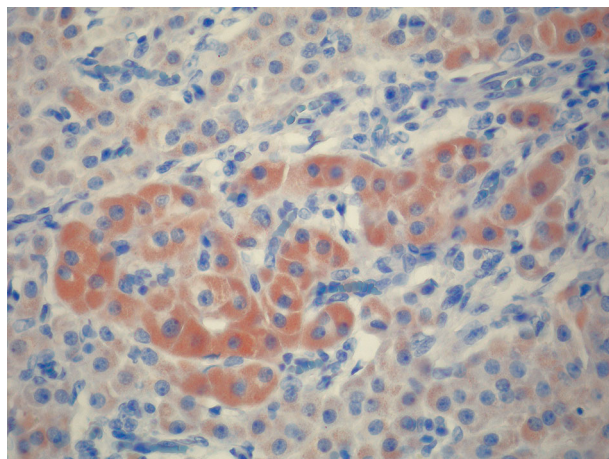


Fig. 5. Inhibin- α immunoreactivity within the tumor cells (modified avidin biotin complex method/ABC), 400 \times

serum α fetoprotein (AFP), β human chorionic gonadotropin (β -HCG), and lactate dehydrogenase (LDH) must be within the reference range.

The presenting features are enlarged testis, gynecomastia and sexual dysfunction. But in most cases, patients present with an incidental finding of a testicular mass on scrotal ultrasonography during evaluation of hydroceles or varicoceles or during diagnostic workup for infertility, as in our case. Gianarini *et al.* in a series with 17 patients with no bilateral lesions found that 5 patients (29.4%) presented with primary infertility, 4 (23.5%) with gynecomastia and 2 (11.8%) after selfpalpation of a scrotal mass. In the remaining 6 patients (35.3%) the tumor was incidentally discovered during scrotal ultrasound. A total of 14 tumors (82.4%) were nonpalpable [10]. Prepubertal boys with androgen-secreting tumors may present with signs of precocious puberty. Boys with estrogen-secreting tumors may present with feminizing symptoms such as gynecomastia or breast tenderness. Adults with androgen-secreting tumors are generally asymptomatic. But in adults with estrogen-secreting tumors, loss of libido, erectile dysfunction, and infertility have been observed.

Scrotal ultrasonography is performed to confirm the diagnosis and most of the tumors are hypoechoic and show hypervascularization [9, 10]. MRI may be an alternative diagnostic tool for small nonpalpable Leydig cell tumors not otherwise visible on sonograms. If malignancy is suspected CT scanning of the abdomen and chest radiography are indicated. Bilateral testicular tumor was detected by scrotal Doppler ultrasound in our case.

As in all intrascrotal tumors, the final diagnosis is based on the histopathological findings after removal of the tumor. Macroscopically, Leydig cell tumors present as well-circumscribed, yellow to brown masses within the testicle. Microscopically, these tumors are composed of large, closely packed cells with eosinophilic cytoplasm, bland nuclei, and small nucleoli. Reinke crystals are pale staining, cylindrical, rectangular, or rhomboid inclusions that are pathognomonic for Leydig cell tumors and are found in up to 30% of patients with such tumors. All definitive diagnoses interpreted the neoplasia as benign LCT using the criteria originally proposed

by Kim *et al.*, which included dimensions (maximum neoplasia diameter), the presence of infiltrating margins and extratesticular extension, atypias, the presence of necrosis and of angioinvasion, and high mitotic index [11].

Leydig cell tumors have been primarily managed with radical inguinal orchiectomy [6, 9, 12]. However, conservative management with testis sparing surgery in younger adults and children were reported in the literature [8, 10]. Inguinal orchiectomy should be performed with early control of the spermatic cord and without violation of the scrotal skin. Testis sparing surgery with enucleation of the mass has been reported in children and younger adults in order to maintain fertility [13–15]. Bilateral radical orchiectomy was performed in our case; because both tumors originated from the mediastinum testis, testis sparing surgery could not be performed.

Chemotherapy with the bleomycin-etoposide-platinum regimen used for germ cell malignancies has limited efficacy in managing malignant Leydig cell tumors. The tyrosine kinase inhibitor imatinib has shown some chemotherapeutic activity in animal models, although this was not demonstrated in human trials [16]. No known role exists for radiation therapy in malignant Leydig cell tumors.

Observation is sufficient in patients in whom a benign Leydig cell tumor is treated with radical inguinal orchiectomy. Patients with malignant tumors require regular follow-up imaging, including CT scanning of the chest and abdomen [9]. Metastases most frequently involve the retroperitoneal lymph nodes. Other reported metastatic sites include the liver (45%), lungs (40%), and bone (25%) [17]. In the review of the literature, there is no proven treatment of choice in case of progressive disease making any one superior to the others (surgery, radiotherapy and chemotherapy) [17]. On the other hand, when there are no metastases and there is no evidence of malignancy, a regular follow-up is preferred by clinical examination, CT scan or ultrasound of the abdomen and by measuring the testosterone and estradiol levels because of the risk of metastases many years after orchiectomy even in a histologically bland tumor [9].

Late onset of metastasis, up to 8 years after orchiectomy, has been reported, which supports the recommendation of long-term tumor surveillance for 10–15 years after surgery [12].

The prognosis for benign Leydig cell tumors is excellent. The mean survival in patients with a malignant variant is 2–3 years [2, 3, 18].

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Submitted: 25.05.2011

Accepted: 23.01.2012