SAGE Open Medical Case Reports
Volume 11: 1–5

DOI: 10.1177/2050313X231184180
journals.sagepub.com/home/sco
Sage

An insight into metastatic Leydig cell tumors: A case report

Jerel David[1], Vaibhav Chumbalkar[2] and Juskaran Chadha[1]

Abstract

Sex cord-stromal tumors comprise approximately 5% of all testicular tumors, while the remainder are of germ cell origin. Leydig cell tumors are the most common subtype of testicular sex cord-stromal tumors and account for 1%–2% of all testicular tumors. Leydig cell tumors are mostly benign but approximately 5%–10% of them have malignant potential. The commonest metastatic sites are regional lymph nodes, lung, liver, and bones. Here, we report a case of late metastatic relapsed Leydig cell disease in a 73-year-old male. The goal of this care report was to better understand manifestation and management of patients with late relapsed Leydig cell tumors and low-volume disease. Patients with metastatic Leydig cell tumors (or sex cord-stromal tumors) have poor prognosis, and standard treatment recommendations do not exist. Surgical resection of metastasis and/or chemotherapy with bleomycin, etoposide, and cisplatin should be discussed with patients, as some were reported to have complete remission after these interventions. Although there are few literature studies and data to support ideal management, this case has shown that there may be utility for local radiation therapy in unresectable low-volume metastatic Leydig cell disease. A limitation in this report is that we will need long-term follow-up regarding this case. Given the rare occurrence of this malignancy, more data collection going forward will assist in the optimal management of future patients, given this diagnosis.

Keywords

Oncology, pathology, palliative, urology

Date received: 14 January 2023; accepted: 6 June 2023

Introduction

Leydig cell tumors (LCTs), which make up 5% of sex cord-stromal tumors (SCSTs), are the most prevalent and arise from the same Leydig cells that typically occupy the interstitium of testicles and secrete testosterone in the presence of luteinizing hormone. They are typically benign tumors, with only 5%–10% being deemed malignant, and have a bimodal distribution with peaks in the prepubertal age group and between the ages of 30 and 60 years.[1] These tumors can present themselves in a variety of ways, ranging from asymptomatic disease to locally invasive and metastatic disease. LCTs can be difficult to diagnose, necessitating a combination of clinical, imaging, and histological analysis. LCTs can be treated surgically, with radiation therapy, or with hormone therapy.[2,3]

We provide a rare instance of a late metastatic relapsed Leydig cell disease in a 73-year-old male in this case report, highlighting the diagnostic and treatment approaches throughout the course of the illness. Only 1% of individuals are likely to experience a very late recurrence of testicular germ cell tumors, which is defined as developing more than 5 years after the initial presentation, and it usually comes with an unfavorable prognosis.[4] The purpose of this report was to provide insight into the clinical course and management of LCTs, which can aid in the diagnostic and treatment decision-making process for other healthcare professionals.

Case presentation

A 73-year-old Caucasian male initially was diagnosed with testicular cancer that was treated with a left orchiectomy at the age of 59 years. Pathology showed an LCT, a subtype SCST measuring 4.2 cm in size and was completely encapsulated,

[1]Department of Hematology and Oncology, Moffitt Cancer Center, Tampa, FL, USA
[2]Department of Pathology, Moffitt Cancer Center, Tampa, FL, USA

Corresponding Author:
Jerel David, Department of Hematology and Oncology, Moffitt Cancer Center, Tampa, FL, USA.
Email: Jerel.David@moffitt.org

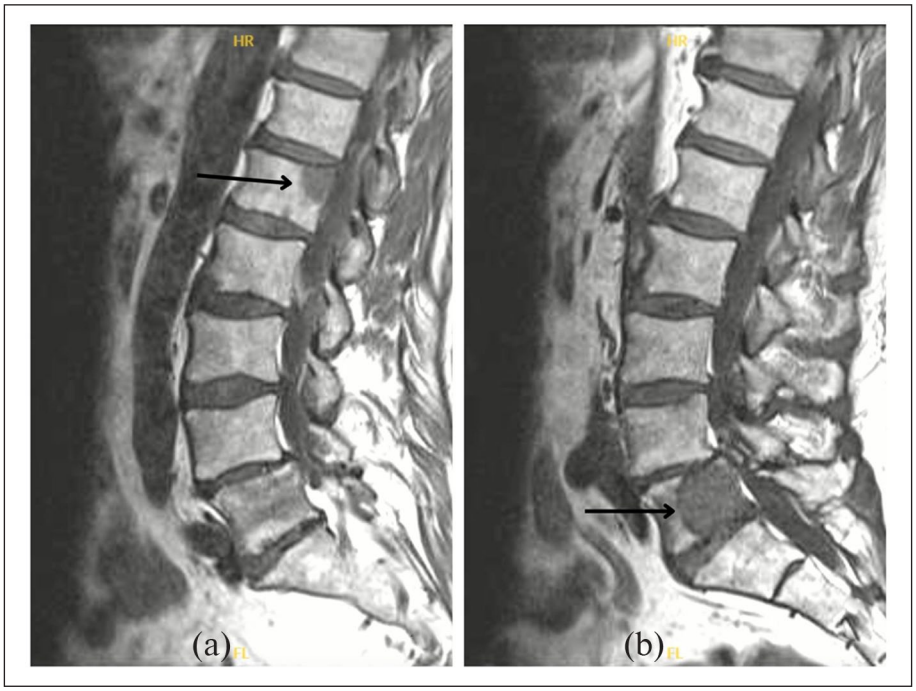

Figure 1. MRI spine: bony metastatic lesion (a) involving L1 and (b) more extensively involving L5 with minimal/mild epidural tumor extension.

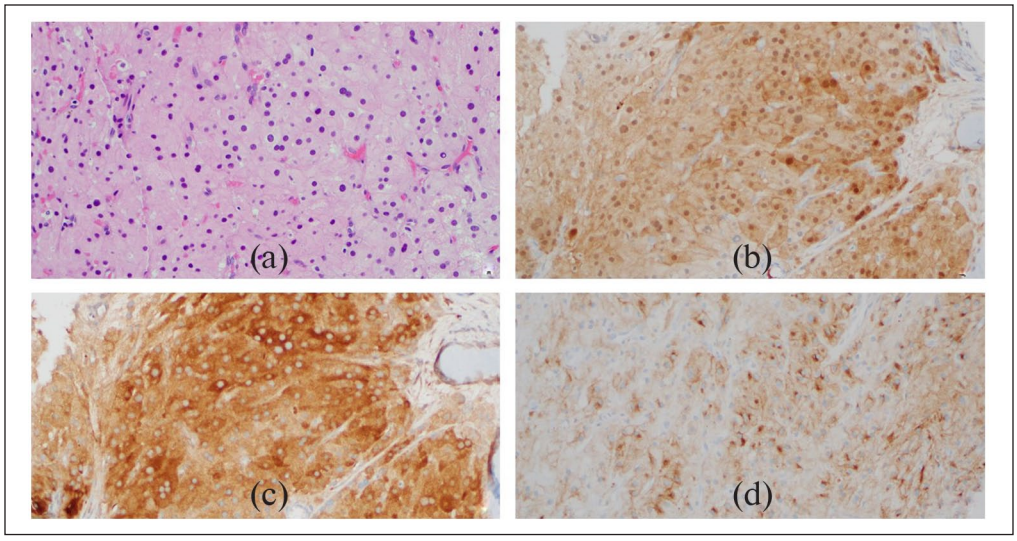

Figure 2. L5 lesion biopsy: (a) H&E-stained section shows plump polygonal cells with abundant cytoplasm with many prominent nucleoli. Immunohistochemical stains performed show staining pattern consistent with Leydig cell tumor that includes positive staining for (b) calretinin, (c) α-inhibin, and (d) synaptophysin (patchy).

with no lymphovascular invasion, and negative for extratesticular involvement. After doing well for many years, the patient presented for progressive lower back pain for 2 months. Patient underwent a magnetic resonance imaging (MRI) of the thoracic and lumbar spine that demonstrated findings worrisome for osseous metastatic disease at L1 and L5 levels (Figure 1). The patient then subsequently underwent a biopsy of the L5 vertebral body. A metastatic lesion comprising polygonal plump cells with abundant cytoplasm and prominent nucleoli was noted (Figure 2(a)). Immunohistochemistry (IHC) performed showed that these cells were positive for calretinin, α-inhibin, synaptophysin (Figure 2(b) and (d)), melan-A, chromogranin, vimentin (not shown), and Ki-67 proliferative index of 7% consistent with LCTs. The tumor was negative for CK AE 1/3, AFB, CK 20, CK7, EMA, S100, WT1, arginase-1, SALL-4, and SOX10.

The patient was discussed at the multidisciplinary genitourinary tumor board, and based on the history and diagnostic information, it was determined that the patient had late metastatic relapse to the vertebra. A comprehensive workup for germ cell tumor markers was unrevealing, and imaging of the right testicle with ultrasound was negative. The patient underwent stereotactic radiosurgery (SRS) to the L5 spinal region with 18 gray (Gy). About 4 months after treatment, patient underwent restaging with a computed tomography (CT) thorax, abdomen, and pelvis. The image findings were described as unchanged and stable bone metastasis in L5 and possibly L1. The patient's tissue was sent for genomic testing, and blood was sent for analysis of cell-free DNA. Tissue testing was unrevealing as the tumor mutation burden (TMB) was low (0 mutations per megabase), Microsatellite instability (MSI) was stable, and PD-L1 was undetectable. Liquid testing showed NTRK1 N356K (K (2.1% variant of uncertain significance), TMB (low 6.7 mutations per megabase) and stable MSI. Given that the patient's disease was overall stable and low volume, he remained on active surveillance. The patient was observed for approximately a year with imaging studies periodically. One month post-SRS, imaging showed a mild enlargement of a left periaortic lymph node from 0.9 to 1.4 cm without any new sites of disease on CT thorax, abdomen, and pelvis. This was followed up with an MRI of the abdomen and this periaortic lymph node was unchanged in size. The patient was reevaluated by radiation oncology for possible stereotactic body radiation (SBRT) to this left para-aortic lymph node; however, the patient remained on active surveillance due to low-volume disease.

Discussion

Testicular neoplasms are classified into two major groups: germ cell tumors (GCTs) and sex stromal cord tumors (SCSTs). SCSTs are derived from Leydig cells, Sertoli cells, granulosa cells, or rarely theca cells.[5] Leydig cell hyperplasia and other neoplasms, such as lymphoma, plasmacytoma, and, in rare cases, a Sertoli cell or GCT, are included in the differential diagnosis for an LCT. Although Sertoli cell tumors can also be immunoreactive with inhibin, most GCTs and somatic tumors can be distinguished from each other by immunohistochemical labeling with inhibin (inhibin-A).[6]

The pathologic diagnosis of LCTs is usually made based on morphologic characteristics of the tumor cells. Pathologists must be familiar with the diagnostic histopathologic features, immunohistochemical panel of this tumor, and its principal differential diagnoses to prevent tumor misdiagnosis.[2] The IHC for LCTs showed diffuse cytoplasmic positivity for calretinin, inhibin, vimentin, melan-A, and negative immunostaining with cytokeratin alpha-fetoprotein (AFP).[2] In this case, IHC staining of the L5 biopsy was positive for calretinin, chromogranin, synaptophysin, vimentin, melan-A, and α-inhibin.

LCTs appear as monomorphic sheets or nests of large cells under a microscope. These cells are round with increased eosinophilic cytoplasm and regular nuclei with a conspicuous nucleolus. Occasionally, they may contain spindle-shaped cells or cytoplasm with vacuoles. About one-third of the time, Reinke's eosinophilic crystals can be observed in the cytoplasm; however, they may be quite sparse and unnoticeable. These crystals, which may also be distinguished by electron microscopy, are typical of Leydig cells but do not indicate neoplasia.[7]

Tumors of the Leydig cell comprise 1%–3% of all testicular neoplasms, but they are the most common interstitial neoplasms of the testis.[8] Testicular LCTs have a bimodal distribution, as they are common in prepubertal boys (most often between 5 and 10 years of age) and in men aged 30–60 years.[3] The risk factors and etiology for LCT are unclear. The mechanism of Leydig cell oncogenesis is still poorly understood. The disruption of the hypothalamic–pituitary–testicular axis leading to excessive stimulation of Leydig cells by excess luteinizing hormone is thought to play a role. Activating mutation in the guanine nucleotide-binding protein α gene is a cause of adult LCTs, by driving tumor development and causing hyperactivity of the testosterone biosynthetic pathway.[9]

The typical presentation in a child would be precocious puberty. The classical clinical presentation in an adult is typically asymptomatic as excess androgen would rarely cause symptoms and estrogen-secreting tumors would present with decreased libido and sexual dysfunction. In this case, the patient initially presented with a palpable testicular mass at the age of 59 years. A scrotal ultrasound is the diagnostic imaging tool of preference, as it has a high sensitivity for diagnosing testicular tumors (98%–100%).[10] LCTs typically appear as hypoechoic and hypervascular lesions on ultrasound.

LCTs are generally benign tumors with only 5%–10% being considered malignant.[11] Malignant behavior has not been described in young males. The commonest metastatic sites are regional lymph nodes, the lung, liver, and bones.[8] At the time of diagnosis, there has been a reported 20% occurrence of the metastatic disease and 40% metastatic involvement within 2 years from diagnosis.[12] In our case, the patient was found to have late metastatic relapse to vertebrae over 10 years after initial diagnosis and treatment. Just 1% of individuals will experience a very late recurrence of testicular germ cell tumors, defined as happening more than 5 years after the original presentation, and it is usually associated with a poor prognosis.[4]

The presence of risk factors or protective factors for metastasis should be disclosed by pathological workup to distinguish between benign and malignant LCTs. Kim et al.[3] examined five metastatic LCTs in adult males and found that at least four of the six major indicators of malignancy (>3 mitoses/10 high-power fields (HPFs), size >50 mm, infiltrative boundaries, nuclear atypia, vascular invasion, and necrosis) were consistently present. These parameters were selected by use of an inferential analysis based on univariate logistic regression models to develop the Leydig cell tumor

scaled score (LeSS) for a predictive model of the metastatic risk. All histologically and clinically benign LCTs were appropriately recognized by a LeSS of 4. All malignant LCTs were accurately recognized with a LeSS of 4.[13] It is unclear if this criterion was applied to the patient's initial diagnosis when the disease was localized. The patient in this case had 4.2 cm in primary tumor which was completely encapsulated, with no lymphovascular invasion, and negative for extratesticular involvement. These characteristics overall would hint at a low chance for disease recurrence.

Systemic chemotherapy or radiation therapy has a limited role in patients with unresectable metastatic disease, as these treatments have low response rates.[14] Active testicular germ cell regimens such as bleomycin, etoposide, and cisplatin (BEP) have been relatively ineffective, with only transient responses. Per the analysis of case series data by Fankhauser et al.,[14] only 6% of patients experienced the complete response after BEP or other platinum-based regimens. A partial response was described in 31% of patients. Of the patients that underwent surgery, 15% had a complete response. The data for radiotherapy are limited, but the Fankhauser et al.[14] case series described a partial response using local therapy to treat supraclavicular nodes. In two other instances, radiation was performed for palliative pain relief.[9,10] A total of eight patients reviewed in Osbun et al.[15] presented at stage II/III. Their outcomes were poor. Six of the eight patients died despite additional surgery, chemotherapy, or radiotherapy. Once again suggests that LCTs appear to be resistant to most chemotherapy regimens, and the goal of radiotherapy was primarily for palliation. In this case, the patient was treated with local radiation therapy to the L5 of the spine.

In this case, the expectation was for pain control and possibly improved disease control to prevent further progression of disease. On subsequent follow-up, the patient's symptoms have been relieved with stable post-radiation changes on imaging.

Conclusion

Patients with metastatic LCTs (or SCSTs) have poor prognosis, and standard treatment recommendations do not exist. Surgical resection of metastasis and/or chemotherapy with BEP should be discussed with patients, as some were reported to have complete remission after these interventions. Although there are few literature studies and data to support ideal management, this case has shown that there may be utility for local radiation therapy in unresectable low-volume metastatic Leydig cell disease. A limitation in this report is that we will need long-term follow-up regarding this case. Given the rare occurrence of this malignancy, more data collection going forward will assist in the optimal management of future patients, given this diagnosis.

Acknowledgements

The authors thank their colleagues from the Department of Pathology, H. Lee Moffitt Cancer Center for providing the slides. They also thank Radiation Oncology for their role in the management of this patient.

Author contributions

The authors confirm contribution to the article as follows: Juskaran Chadha helped in case conception and design; Vaibhav Chumbalkar contributed to the analysis and interpretation of pathology results; Jerel David prepared the draft manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Jerel David https://orcid.org/0000-0003-4379-734X

References

1. Mooney KL and Kao CS. A contemporary review of common adult non-germ cell tumors of the testis and paratestis. *Surg Pathol Clin* 2018; 11: 739–758.
2. Al-Agha OM and Axiotis CA. An in-depth look at Leydig cell tumor of the testis. *Arch Pathol Lab Med* 2007; 131: 311–317.
3. Kim I, Young RH and Scully RE. Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. *Am J Surg Pathol* 1985; 9: 177–192.
4. Moore JA, Slack RS, Lehner MJ, et al. Very late recurrence in germ cell tumor of the testis: lessons and implications. *Cancers* 2022; 14: 1127.
5. Ober WB and Sciagura C. Leydig, Sertoli, and Reinke: three anatomists who were on the ball. *Pathol Annu* 1981; 16(Pt. 1): 1–13.
6. Iczkowski KA, Bostwick DG, Roche PC, et al. Inhibin A is a sensitive and specific marker for testicular sex cord-stromal tumors. *Mod Pathol* 1998; 11: 774–779.
7. Ulbright TM, Kao C-S, Williamson SR, et al. *Tumors and tumor-like lesions of the testis and adjacent tissues*. Arlington, VA: American Registry of Pathology, 2022.
8. Rich MA and Keating MA. Leydig cell tumors and tumors associated with congenital adrenal hyperplasia. *Urol Clin North Am* 2000; 27: 519x–528.
9. Boot AM, Lumbroso S, Verhoef-Post M, et al. Mutation analysis of the LH receptor gene in Leydig cell adenoma and hyperplasia and functional and biochemical studies of activating mutations of the LH receptor gene. *J Clin Endocrinol Metab* 2011; 96: E1197–E1205.

10. Acar C, Gurocak S and Sozen S. Current treatment of testicular sex cord-stromal tumors: critical review. *Urology* 2009; 73: 1165–1171.
11. Pomajzl AJ and Siref LE. *Leydig cell cancer*. Treasure Island, FL: Statpearls, 2023.
12. Bertram KA, Bratloff B, Hodges GF, et al. Treatment of malignant Leydig cell tumor. *Cancer* 1991; 68: 2324–2329.
13. Colecchia M, Bertolotti A, Paolini B, et al. The Leydig cell tumour scaled score (LeSS): a method to distinguish benign from malignant cases, with additional correlation with MDM2 and CDK4 amplification. *Histopathology* 2021; 78: 290–299.
14. Fankhauser CD, Grogg JB, Hayoz S, et al. Risk factors and treatment outcomes of 1,375 patients with testicular Leydig cell tumors: analysis of published case series data. *J Urol* 2020; 203: 949–956.
15. Osbun N, Winters B, Holt SK, et al. Characteristics of patients with Sertoli and Leydig cell testis neoplasms from a National Population-Based Registry. *Clin Genitourin Cancer* 2017; 15: e263–e266.