Retroperitoneal Leydig cell tumor recurrence presenting 14 years after orchiectomy

Nicholas H. Chakiryan, MD,[1] Phil W. Raess, MD,[2] Kevin Turner, MD,[2] Jason C. Hedges, MD,[1] Jen-Jane Liu, MD[1]

[1]Department of Urology, Oregon Health & Science University, Portland, Oregon, USA
[2]Department of Pathology, Oregon Health & Science University, Portland, Oregon, USA

CHAKIRYAN NH, RAESS PW, TURNER K, HEDGES JC, LIU J-J. Retroperitoneal Leydig cell tumor recurrence presenting 14 years after orchiectomy. *Can J Urol* 2018;25(1):9210-9213.

Malignant Leydig cell tumor is a rare entity that has been previously described as rapidly progressive and uniformly fatal. We present the case of a malignant Leydig cell tumor that presented 14 years after orchiectomy with an isolated retroperitoneal metastasis. Our patient underwent a retroperitoneal lymph node dissection and has been free of recurrence or progression at 12 months of follow up. Additionally, we describe the symptomatic hormone dysfunction experienced by our patient as a result of his tumor.

Key Words: orchiectomy, malignant Leydig cell tumor, recurrence

Introduction

Leydig cell tumor (LCT) is a rare testicular neoplasm, comprising approximately 1%-3% of all testicular neoplasms, with malignant LCTs making up 7%-10% of these cases.[1] Malignant LCT occurs exclusively in adults, is poorly responsive to chemotherapy or radiation, and carries a poor prognosis, with two thirds of patients dying within 2 years.[2] Recurrence typically presents early and is usually fatal. Due to its rarity, there are currently no guidelines for surveillance or treatment of stage I LCT, although it has been suggested that retroperitoneal lymph node dissection (RPNLD) may be warranted in patients with high risk features.[3,4] We present a case of isolated retroperitoneal LCT recurrence diagnosed 14 years after orchiectomy.

Case report

A 63-year-old male with a history of LCT diagnosed after right radical inguinal orchiectomy in 2002 for a testicular mass presented 12 years later with abdominal pain. A 10 cm paracaval mass was identified on CT scan of the abdomen. The patient's history of orchiectomy and LCT were not elicited at the time. CT guided biopsy of the paracaval mass was performed, but the pathology showed only red blood cells and necrotic debris. The patient was then lost to follow up, and presented 2 years later to

Accepted for publication November 2017

Address correspondence to Dr. Nicholas Chakiryan, Department of Urology, Oregon Health & Science University, Mail Code CH10U, 3303 SW Bond Avenue, 10th Floor, Portland, OR 97239 USA

a urologist for evaluation of the mass as a result of continued symptoms. CT scan of the abdomen and pelvis revealed that the mass had grown to 12 cm in size, Figure 1. CT scan of the chest was negative for pulmonary metastases. There was significant mass effect on his vena cava and duodenum, and he had bilateral lower extremity swelling. He also exhibited symptoms of hypersexuality and emotional lability. Total serum testosterone was measured at 3303 ng/dL, with undetectable LH and FSH levels. LDH, β-HCG, and AFP were within normal limits. He was successfully treated with bicalutamide, 50 mg PO every other day for his androgen excess, with improvement of his symptoms. CT-guided percutaneous biopsy of the mass confirmed LCT.

He underwent uneventful open bilateral full template RPLND. There was no gross invasion of surrounding structures intraoperatively. Gross examination revealed an 11 cm circumscribed, homogeneous tan mass with areas of necrosis. On histologic examination the tumor was composed of epithelioid cells with large, round nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. The tumor had a solid growth pattern and a circumscribed border. Although the primary testicular Leydig cell tumor was not available for review, high grade features were evident in the retroperitoneal tumor, including moderate cytologic atypia, necrosis, and increased mitotic activity (11 mitoses per 10 high power fields). No angiolymphatic invasion was identified, Figure 2. There were an additional 27 lymph nodes that were negative for malignancy.

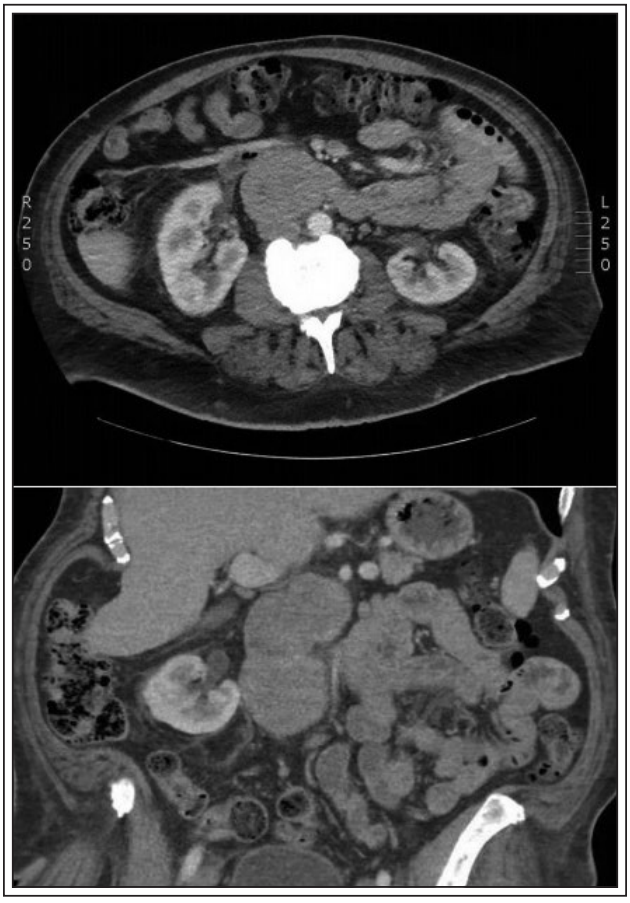

Figure 1. CT abdomen and pelvis shows a 12 cm pracaval mass closely associated with the IVC and duodenum.

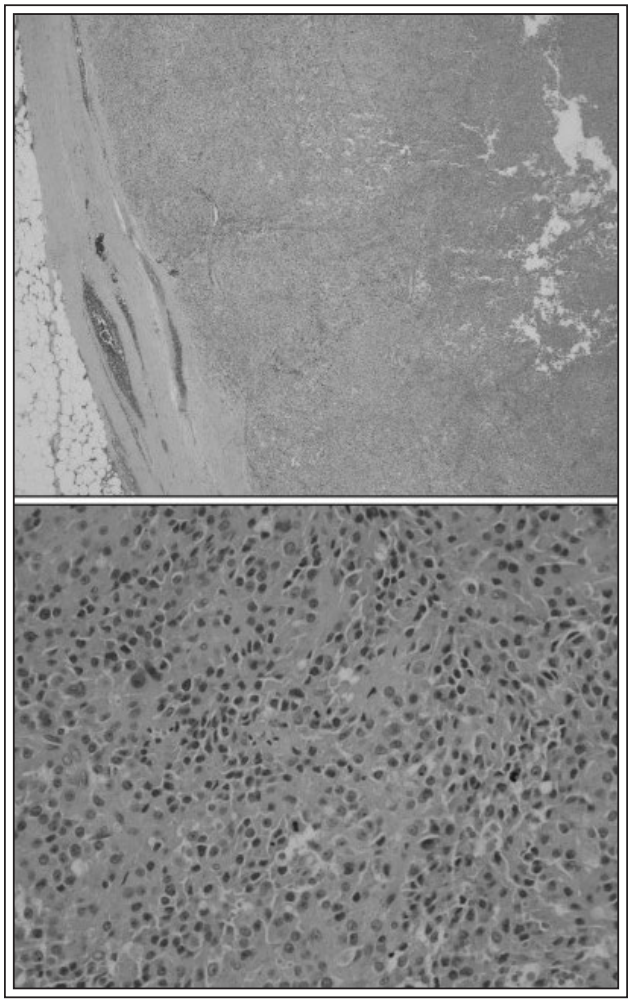

Figure 2. Microscopic examination of the resected retroperitoneal mass shows epithelioid cells with large, round nuclei, with prominent nucleoli and abundant eosinophilic cytoplasm, consistent with Leydig cell tumor. High grade features are evident in the retroperitoneal tumor, including moderate cytologic atypia, necrosis, and increased mitotic activity (11 mitoses per 10 high power fields). No angiolymphatic invasion was identified.

TABLE 1. **Perioperative testosterone and gonadotropins**

	Total testosterone (ng/dL)	LH (mLU/mL)	FSH (mLU/mL
Preoperative	3303	< 1	< 1
Postoperative day 3	260	< 1	< 1
Postoperative day 12	26	< 1	< 1
Postoperative day 66	175	19.9 (H)	12.9 (normal)
Postoperative day 117	202	21.3 (H)	14.3 (normal)

His postoperative course was uncomplicated and he was discharged on postoperative day 3. Bicalutamide was discontinued prior to discharge. Immediate postoperative values of total testosterone, LH, and FSH were low, and he was asymptomatic at the time, Table 1.

At his postoperative visit 2 weeks after surgery he endorsed severe depression, tearfulness, and decreased motivation. Total serum testosterone had further decreased to 26 ng/dL, with undetectable LH and FSH levels. One month later his symptoms were improved, with a total serum testosterone of 175 ng/dL, LH of 19.9 mIU/mL, and FSH of 12.9 mIU/mL. Clomiphene citrate 50 mg PO daily was recommended to enhance recovery of hypothalamus-pituitary-gonadal axis function, however, the patient declined due to cost of the medication. Total serum testosterone continued to improve without pharmacologic intervention, with an appropriate rise in LH levels. CT imaging at 3, 8, and 12 months post-surgery did not show evidence of recurrence or progression of disease.

Discussion

Testicular cancer is uncommon, comprising less than 1% of all malignancies, with LCT representing only 1%-3% of testicular neoplasms.[5] Since only 7%-10% of LCTs are malignant, it is rare for urologists to encounter this diagnosis. LCTs and Sertoli cell tumors are derived from sex cord stromal tissue, in contrast with germ cell tumors (GCTs), which comprise the vast majority of testicular cancers. Sex cord stromal tumors are most common in the fifth decade of life, compared to GCTs, which commonly present in the second and fourth and have a bimodal distribution.[6,7] LCTs are usually locally confined at presentation, although metastases have been observed.[8]

Due to the rarity of LCT, there are no guidelines for management, and recommendations for surveillance and management are largely based on case reports and small retrospective studies. LCT is generally staged similarly to germ cell testicular malignancies, although the clinical course may differ. Patients with stage I tumors are largely surveilled after orchiectomy given that the majority of LCTs are not malignant. It has been suggested that patients with two or more high risk features seen on pathology should undergo primary RPLND, as these patients may be more prone to metastases and recurrence.[3] High risk features include tumor greater than 5 cm, necrosis, moderate or severe nuclear atypia, angiolymphatic invasion, infiltrating margins, and greater than 5 mitotic features per 10 high power fields.[9] In a series of 28 patients with LCTs from Memorial Sloan Kettering Cancer Center, those that demonstrated two or more high risk features were treated with primary RPLND.[3] Of patients with fewer than two high risk features, none developed metastases, although follow up was short (median = 14 months). Furthermore, patients that presented with clinically apparent nodal metastases all recurred between 3 to 8 months after RPLND and ultimately died of their disease. Similar findings were demonstrated in a separate study from Indiana University, in which six patients with LCT underwent unilateral or bilateral RPLND. Three of the six patients had stage I disease, and were all alive and without disease at a median follow up of 3 years. However, the remaining patients who were found to have stage II disease on RPLND all eventually died of their disease, with a median survival of 25 months.[10] Primary RPLND for all sex cord stromal tumors with two or more high risk features is recommended by the authors. Upon review of the subgroups of specific pathologies, the vast majority of patients with metastatic LCT ultimately die of their disease, regardless of whether RPLND was performed in a primary fashion.[3,10]

Previous literature suggests that the majority of malignant LCTs present early with multiple sites of metastasis, progress quickly, are refractory to chemo- and radiation therapy, and are fatal within 2 years.[2,3] Our patient challenges these assumptions, as he

presented 14 years after orchiectomy with an isolated retroperitoneal metastasis. To our knowledge, this is the longest reported time from orchiectomy to recurrence for malignant LCT. Grem et al reported a patient who recurred in the contralateral testicle 5 years after initial orchiectomy, and then 4 years following the orchiectomy, developed retroperitoneal disease.[1]

Our patient's initial orchiectomy specimen was not available for review, so we were not able to assess high risk features within the original specimen. The retroperitoneal metastasis had three high risk features: moderate nuclear atypia, necrosis, and > 5 mitotic figures per high powered field. At the time of this report 12 months post-surgery, he is free of disease. Based on the existing literature, he is likely to develop progression of his disease in the setting of nodal metastases, although the slow progression of his disease process is unusual, and may suggest a less aggressive clinical course. Interestingly, the patient was known to have large volume retroperitoneal disease for at least 2 years from the initial time of diagnosis, without evidence of progression, suggesting he may have an indolent disease course.

Review of the literature did not reveal any established recommendation for management of hormonal dysfunction in the setting of LCT, although it is not surprising that rapid and large shifts in testosterone levels would have a significant clinical impact on the patient's mood. We were able to successfully manage our patient's preoperative hyperandrogenergic symptoms with bicalutamide, an androgen receptor antagonist that is well described in the setting of androgen deprivation therapy for prostate cancer. Resection of his recurrent LCT caused prompt withdrawal of autonomous extratesticular testosterone, resulting in a hypogonadotropic hypogonadal state, presumably due to chronic feedback inhibition of the release of GnRH, LH, and FSH from the hypothalamus and pituitary secondary to elevated testosterone. Our patient spontaneously recovered intrinsic activity within 2 months, accompanied with resolution of symptoms.

Conclusion

LCT can recur after a prolonged period with retroperitoneal metastases, although the clinical course may be more indolent. Patients with LCT may experience clinically significant hormonal dysfunction both pre and postoperatively. Patients with elevated testosterone and low gonadotropins are at a risk for severe hypogonadism postoperatively due to central depression of the hypothalamus-pituitary-gonadal axis. □

References

1. Grem JL, Robins HI, Wilson KS, Gilchrist K, Trump DL. Metastatic Leydig cell tumor of the testis. Report of three cases and review of the literature. *Cancer* 1986;58(9):2116-2119.
2. Bertram KA, Bratloff B, Hodges GF, Davidson H. Treatment of malignant Leydig cell tumor. *Cancer* 1991;68(10):2324-2329.
3. Silberstein JL, Bazzi WM, Vertosick E et al. Clinical outcomes of local and metastatic testicular sex cord-stromal tumors. *J Urol* 2014;192(2):415-419.
4. Hendry J, Fraser S, White J, Rajan P, Hendry DS. Retroperitoneal lymph node dissection (RPLND) for malignant phenotype Leydig cell tumours of the testis: a 10-year experience. *SpringerPlus* 2015;4(1):20.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(1):7-30.
6. Osbun N, Winters B, Holt SK, Schade GR, Lin DW, Wright JL. Characteristics of patients with sertoli and Leydig cell testis neoplasms from a national population-based registry. *Clin Genitourin Cancer* 2017;15(2)e263-e266.
7. Banerji JS, Odem-davis K, Wolff EM, Nichols CR, Porter CR. Patterns of care and survival outcomes for malignant sex cord stromal testicular cancer: results from the national cancer data base. *J Urol* 2016;196(4):1117-1122.
8. Featherstone JM, Fernando HS, Theaker JM, Simmonds PD, Hayes MC, Mead GM. Sex cord stromal testicular tumors: a clinical series--uniformly stage I disease. *J Urol* 2009;181(5): 2090-2096.
9. Kim I,Young RH, 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(3):177-192.
10. Mosharafa AA, Foster RS, Bihrle R et al. Does retroperitoneal lymph node dissection have a curative role for patients with sex cord-stromal testicular tumors? *Cancer* 2003;98(4):753-757.