



Case report

Bilateral congenital cryptorchidism and unilateral Leydig cell tumor in an adult presenting with gynecomastia and primary infertility: A case report

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ABSTRACT

Introduction and importance: The neoplasms of the testis are sporadic tumors among men. Furthermore, the rarest subset of these is neoplasms belonging to the stromal tumors of the sex cord. Leydig cell tumors are the most common form among the testicular stromal tumors. In our case, the underlying risk factor associated with the development of Leydig cell tumors was cryptorchidism. While mostly unilateral, cases of bilateral cryptorchidism may be present and have been rarely reported.

Case presentation: We report a 36-year-old gentleman who presented to us with the inability to carry off intercourse without difficulty attaining erection on stimulation for the past two years. He had a history of left undescended testis since birth, for which he underwent left orchidopexy 20 years ago. An ultrasound of the pelvis showed an oval hypoechoic-shaped heterogeneous mass in the right mid-inguinal canal. Relevant blood investigations showed a deranged hormonal profile. He then underwent an uneventful right radical orchiectomy, histopathology of which was consistent with Leydig cell tumor.

Clinical discussion: LCT with a history of bilateral cryptorchidism has rarely been reported. This case highlights its clinical presentation, management, and further follow-up in such patients.

Conclusion: Bilateral congenital cryptorchidism may be associated with Leydig cell tumor years later in life hence long-term follow-up is required for these patients. The clinical presentation of these tumors may vary among individuals. Any change in physical appearance, hormonal assay, and imaging studies should promptly be followed for possible surgical resection and close monitoring.

1. Introduction

Neoplasms of the testis account for approximately 1–1.5% of all cancers among men. Furthermore, the rarest subset of these rare neoplasms belongs to the stromal tumors of the sex cord, which correspond to just 4% of all testicular cancers [1]. Among the testicular stromal tumors, Leydig cell tumors (LCTs) are the most common form, accounting for approximately 75% to 80% [2], and overall they account for 1–3% among all testicular tumors in adults. Most of the cases of LCTs are unilateral and benign on presentation [3], whereas only about 3% of cases are found to be bilateral. Distant metastasis is rare and is only found in about 10% of the cases at presentation, with metastasis involving the inguinal lymph nodes and extranodal organs, including the liver, lungs, and bones being the most common sites involved. Histologically, the tumor consists of the proliferation of large polygonal

tumor cells with granular eosinophilic cytoplasm and prominent nucleoli arranged in a pattern of sheets [4].

LCTs have a unique feature of either being hormonally inactive or may secrete various hormones, including testosterone and its derivatives. Patients with LCT may present clinically with a painless or painful testicular mass irrespective of age. However, children may present with precocious pseudo puberty, including unilateral or bilateral gynecomastia, and adults may present with erectile dysfunction, decreased libido, or infertility [5]. According to the review by Efthimiou et al., 480 cases of LCT have been reported in the literature, and among them, 29.2% presented as a testicular mass and 12.5% with gynecomastia [4]. Owing to the remarkable advancement in the use of better ultrasound technologies, the incidence of LCTs seems to be rising, with early detection of testicular incidentalomas requiring further workup.

The etiology of LCTs is not completely understood and appears to be

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multifactorial. In our case, the underlying risk factor associated with LCT development is cryptorchidism, which refers to the absence of one or both testes from the scrotal sac. It is associated with a higher risk for male infertility and testicular cancer [6].

While mostly unilateral, cases of bilateral cryptorchidism may be present and have been rarely reported [7]. Here we report a case of LCT in a young adult male with bilateral congenital cryptorchidism who presented with gynecomastia and infertility.

2. Case presentation

A 36-year-old gentleman with morbid obesity and resident of Quetta, Pakistan, with a primary testicular defect in spermatogenesis, presented initially in our institution in September 2020 with the inability to carry off intercourse without any difficulty in attaining erection on stimulation for the past two years. He also complained of enlarged swellings in both of his breasts for the past three years. He had a history of left undescended testis since birth, for which he underwent left orchidopexy 20 years ago. He did not have any history of smoking or drug abuse. He did not have a family history of malignancy or cryptorchidism.

On general physical examination, all his vital parameters are normal; however, he had visible grade II bilateral gynecomastia as per Simon's classification, which revealed firm masses extending from the nipples. Furthermore, his systemic examination showed a small scrotal sac without palpable testicular swelling. The rest of the systemic examination was unremarkable. A bilateral mammogram was performed, which showed bilateral category O2 lesion on breast imaging-reporting and data system (BIRADS). An ultrasound (U/S) of the pelvis was performed,

which showed an oval hypoechoic shaped heterogeneous mass in the right mid inguinal canal (Fig. 1). Relevant blood investigations were performed, and his hormonal profile revealed serum testosterone level of 375 ng/ml (normal 5-100 ng/ml), Oestradiol levels of 106 pg/ml (normal 0-50 pg./ml), serum prolactin level of 8.1 ng/ml (normal 3-14.7 ng/ml), follicular stimulating hormone (FSH) level of 26.8 mIU/ml (normal 1.4-15.4 mIU/ml) and luteinizing hormone (LH) level of 11.58 mIU/ml (normal 1.2-7.8 mIU/ml). Tumor marker assay showed alpha-fetoprotein (AFP) level of <1.1 IU/ml (normal <6.7 IU/ml) and beta-HCG level of 2 mIU/ml (normal <6.7 mIU/ml). He was advised to follow up in the clinic with further investigation results, however, he lost to follow and later presented in January 2021 with worsening lower abdominal pain and an increase in the size of right testes. A magnetic resonance imaging (MRI) of the pelvis was performed, which showed an empty scrotal sac bilaterally, with an oval-shaped signal intensity focus along the right inguinal canal suggestive of the right ectopic testis, being $3 \times 2.2 \times 2.9$ cm in size, having a small abnormal signal intensity focus with the homogenous enhancement of 2×1.4 cm, highly suggestive of the neoplastic lesion and another abnormal signal intensity area along left inguinal vessels suggestive of left atrophic ectopic testis. U/S penile Doppler showed venous leakage without arterial insufficiency.

His case was discussed in a multidisciplinary tumor board (MDT) meeting, and options regarding close monitoring with history and physical examination along with 3-6 monthly repetition of serum tumor markers, hormonal profile, and imaging studies vs. right orchiectomy and observation for left testis were discussed in detail with the patient however he opted for surgical intervention.

He then underwent an uneventful right radical orchiectomy in

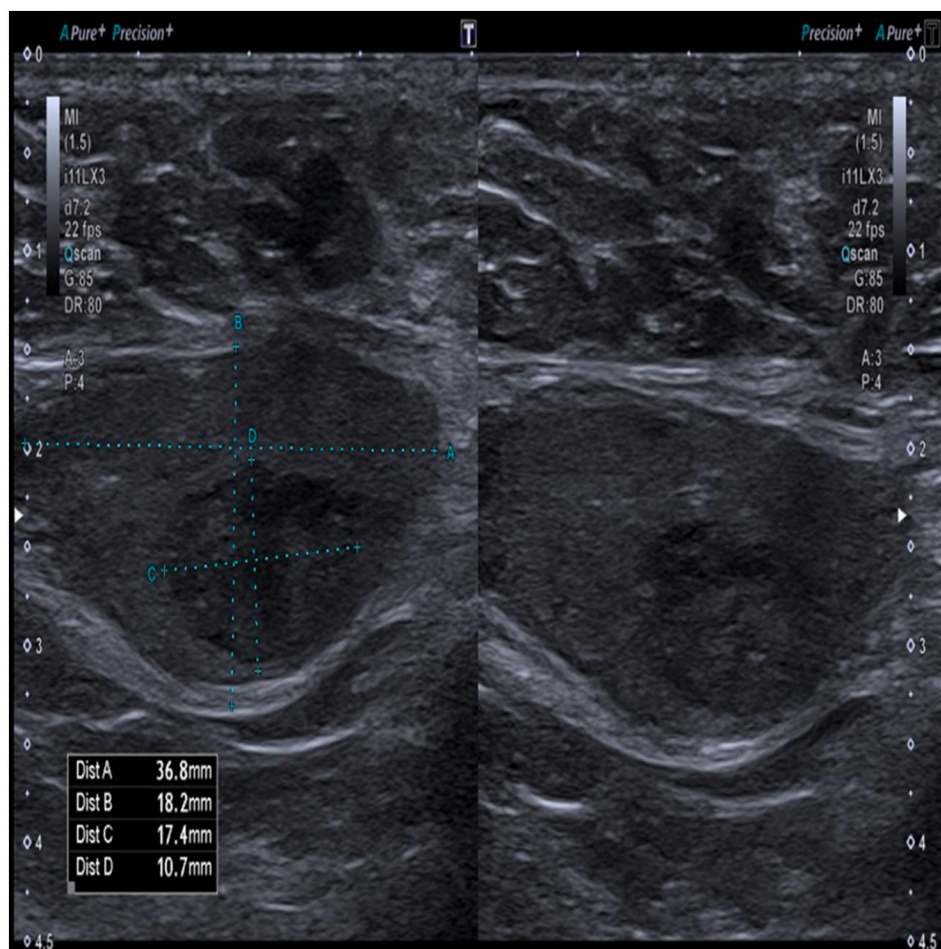


Fig. 1. Hypoechoic oval-shaped heterogeneous mass in mid right inguinal canal, representing undescended right testis.

January 2021 in our institution. Per-operative findings revealed right testis just lateral to the pubic tubercle, being small and floppy without any hard mass, being 1.1×1 cm in size, histopathology of which was consistent with LCT staining positive for melanin A, inhibin, and negative for SALL-4 (Fig. 2), stage I, pT1aN0M0, limited to testes with no involvement of spermatic cord or resected margins and no lymphovascular invasion.

Post-orchietomy, he remained hemodynamically stable hence he was discharged and was initially called to the clinic in one week time for wound assessment later on, he was advised to follow up in the clinic after three months for a physical examination with repeat testosterone levels. Upon clinic visit three months later, his serum testosterone was 104 ng/ml (normal 5-100 ng/ml). He had an empty scrotal sac on physical examination, he had residual grade I gynaecomastia bilaterally and no lymphadenopathy. His weight was static on subsequent follow-up visits. He was then advised to continue surveillance as he had stage I disease without high-risk features. He plans to follow up in 3 months with repeat testosterone levels and imaging studies.

3. Discussion

Primary testicular neoplasms constitute the most common solid organ malignancy seen in young males aged 15 and 35. Certain risk factors are associated with the development of testicular neoplasms, and these include cryptorchidism, hypospadias, family history (first degree relative with testicular tumor), infertility, Klinefelter's syndrome, a history of a contralateral testicular malignancy, and even trauma [8]. They are broadly divided into two categories, namely, germ cell tumors and sex cord-stromal tumors [4]. Germ cell tumors are classified histologically into two broad classes: seminomas and non-seminomas, whereas the sex cord-stromal tumors notably include Leydig cell tumors, Sertoli cell tumors, and granulosa cell tumors.

There are multiple factors associated with the development of LCTs. Cryptorchidism is the most common sexual developmental anomaly of childhood and has been reported in the literature to be associated with LCTs. It is a major causative risk factor in male adult infertility as it exposes the testes to a higher temperature than normal, leading to impaired spermatogenesis. Unilateral cryptorchidism is more common than bilateral cryptorchidism at a ratio of 4:1 [9]. Cases of LCTs with a history of bilateral congenital cryptorchidism have rarely been reported.

As these tumors secrete oestradiol, the absence of testosterone coupled with the significant presence of estradiol leads to the development of gynecomastia and defective in physiological testicular descent, which also leads to infertility, which is of significant concern in these areas patients. Untreated bilateral cryptorchidism is associated with impairment in spermatogenesis, with 100% oligospermia and 75% azoospermia [10].

These tumors are usually associated with the deranged hormonal profile, attributing to the endocrine abnormalities commonly encountered with these tumors. High estrogen, high oestradiol, high luteinizing hormone (LH), high follicle-stimulating (FSH), and low testosterone levels are the most routinely hormonal changes seen upon workup [11]. Rusnak et al. reported that patients with a history of bilateral cryptorchidism, have higher FSH levels and lower testosterone levels compared to those with unilateral cryptorchidism [12]. Tumor markers associated with testicular germ cell tumors are usually negative in patients with Leydig cell tumors. Immunohistochemically, LCTs express positive inhibin and Melan-A but staining for calretinin and vimentin varies [13].

As most cases follow a benign clinical course, adjuvant therapy is not usually warranted, except for the 2.5–15% of LCTs that behave aggressively [11]. Kim et al. first described the six histopathological features of stromal tumors predictive of metastatic potential in 1985. These include tumor size greater than 5 cm, moderate or severe nuclear atypia, vascular or lymphatic invasion, more than five mitoses per high-powered field, necrosis, and infiltrative margins [14]. These features are now applied to only LCTs but also to all testicular sex cord-stromal tumors subtypes.

Surgical resection remains the standard gold treatment for both benign and malignant forms of LCTs [15]. Radical orchietomy, with or without retroperitoneal lymph node dissection (RPLND), is currently recommended as the standard surgical procedure for all benign testicular neoplasms. RPLND is not usually recommended for stage I and benign LCTs. The role of testis-sparing surgery (TSS) has also been evaluated as a reasonable treatment option for benign LCTs. In 2017, Laclergerie et al. compared TSS with the radical orchietomy approach in patients diagnosed with LCT and reported a disease-free survival of 95.2% in TSS versus 77.1% in the orchietomy group *p*-value of 0.23 [16]. Patients with advanced stages, i.e., stage III or stage II tumors demonstrating two or more high-risk features including positive margins, lymphovascular invasion, tumor size >5 cm, or histological signs of

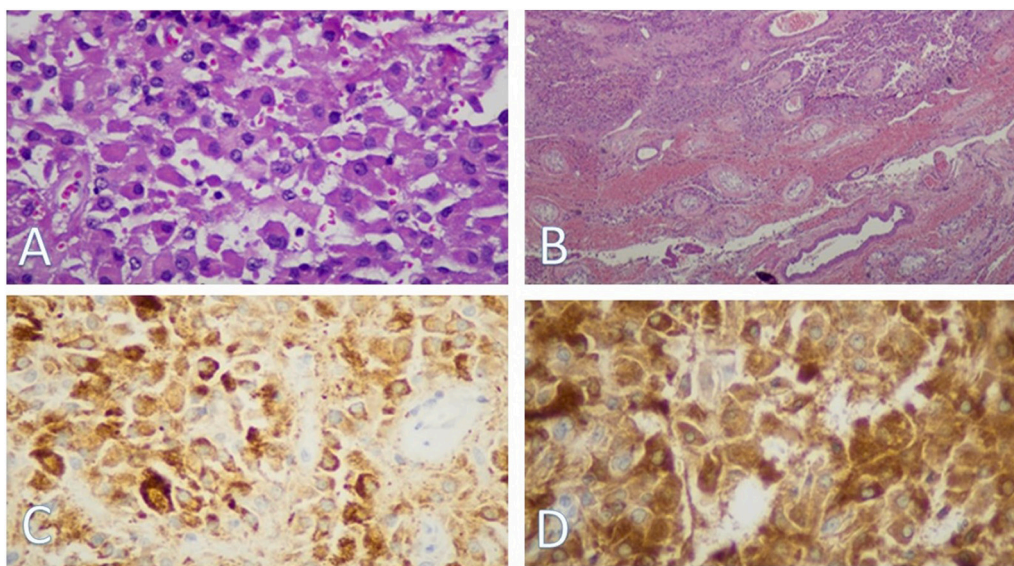


Fig. 2. (A) H&E stain of the neoplastic lesion showing sheets of round to polygonal cells, abundant eosinophilic cytoplasm, eccentrically placed nuclei, open chromatin, and occasional conspicuous nucleoli. (B) H&E stain showing testicular tissue involved by a neoplastic lesion. (C) IHC staining positive for MELAN-A. (D) IHC staining shows diffuse strong positivity for inhibin. (Magnification A, C, D 40 \times & B 20 \times).

malignancy, are managed with radical orchiectomy with early retroperitoneal lymph node dissection [17].

The management of malignant LCTs is controversial as currently, there is no standardized treatment algorithm available. Due to these tumors' increased resistance to chemotherapy and radiotherapy, management options are limited to primary surgical resection, with the bit of therapeutic role of metastasectomy [18]. However, we need more data to establish the standard procedures for managing such patients. The survival rate of stage I is as high as 91% at five years [19]; however, survival of metastatic disease remains dismal, with the median survival rate of one to two years [20].

Our patient had a history of bilateral cryptorchidism unilateral orchidopexy and is now diagnosed with Leydig cell tumor in contralateral testis, having raised FSH levels and low testosterone levels and high oestradiol levels secreted from LCTs, resulting in infertility and gynecomastia, respectively.

4. Conclusions

Bilateral congenital cryptorchidism may be associated with Leydig cell tumor (LCT) years later in life hence long-term follow-up is required for these patients with periodic monitoring of hormonal profile and imaging studies. The clinical presentation of these tumors may vary among individuals and can present with a testicular mass and rarely with gynecomastia or infertility. Any change in physical appearance, hormonal assay, and imaging studies should promptly be followed for possible surgical resection and close monitoring.

Abbreviations

AFP	alpha-fetoprotein
BIRADS	breast imaging-reporting and data system
FSH	follicular stimulating hormone
LCT	Leydig cell tumors
LH	luteinizing hormone
MDT	multidisciplinary tumor board
MRI	magnetic resonance imaging
RLPND	retroperitoneal lymph node dissection
TSS	testis-sparing surgery
US	ultrasound

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

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Research registration

Not applicable.

Guarantor

Corresponding author is the guarantor of this case-report.

Patient perspective

Initially, the patient was reluctant for surgical procedure but then Doctors counseled him and he opted for surgical intervention. He was quite happy and satisfied with the team and treatment.

Declaration of competing interest

The authors declare no conflict of interest.

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References

- [1] R.M. Justo, E. Bernabé, M.C. Ronchini, E. Lucas, G. Saber, L.C.Zd. Silva, Malignant Leydig cell tumor in a 91-year-old man: case report, *Int.Braz. J. Urol.* 45 (2019) 1260–1265.
- [2] C. Pozza, R. Pofi, M. Tenuta, M.G. Tarsitano, E. Sbardella, G. Fattorini, et al., Clinical presentation, management and follow-up of 83 patients with Leydig cell tumors of the testis: a prospective case-cohort study, *Hum. Reprod.* 34 (8) (2019) 1389–1403.
- [3] Wahyudi I. Trahmono, A. Rodjani, G.R. Situmorang, N.S. Marzuki, Precocious pseudo-puberty with testicular enlargement: two cases of Leydig cell tumor with different histopathological results, *Res. Rep. Urol.* 12 (2020) 577–582.
- [4] J. Zhu, Y. Luan, H. Li, Management of testicular Leydig cell tumor: a case report, *Medicine* 97 (25) (2018).
- [5] M.F. Tazi, S. Mellas, M.J. El Fassi, M.H. Farihi, Leydig cell hyperplasia revealed by gynecomastia, *Rev.Urol.* 10 (2) (2008) 164.
- [6] S.W. Leslie, H. Sajjad, C.A. Villanueva, Cryptorchidism. *StatPearls*, StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC, Treasure Island (FL), 2021.
- [7] W. Muncy, R. Dutta, R.P. Terlecki, L.L. Woo, K. Scarberry, Fertility potential in adult men treated for uncorrected bilateral cryptorchidism: a systematic literature review and analysis of case reports, *Andrology* 9 (3) (2021) 781–791.
- [8] M. Nauman, S. Leslie, Nonseminomatous Testicular Tumors, *StatPearls*, 2021.
- [9] D. Tasa, A. Fotoohi, F. Safarnejad, A. Elyasi, A rare case report of undescended testis: both on one side, *Urol. J.* 17 (1) (2020) 105–106.
- [10] B. Stoykov, N. Kolev, V. Dunev, P. Genov, D. Gincheva, M. Georgiev, Successful in vitro fertilization in a 30 years old man with bilateral abdominal cryptorchidism, *Urol.Case Rep.* 31 (2020), 101173.
- [11] H.K. Carroll, T. Nolis, W. Darwish, M. Harrison, J.A. McCaffrey, Leydig cell tumours: a case series from a single Irish centre, *SN Compr.Clin.Med.* 3 (6) (2021) 1307–1312.
- [12] S.L. Rusnack, H.-Y. Wu, D.S. Huff, H.M. Snyder, M.C. Carr, R.D. Bellah, et al., Testis histopathology in boys with cryptorchidism correlates with future fertility potential, *J. Urol.* 169 (2) (2003) 659–662.
- [13] W. Ben Kridis, M. Lajnef, S. Khmiri, O. Boudawara, M.H. Slimen, T. Boudawara, et al., Testicular leydig cell tumor revealed by hydrocele, *Urol.Case Rep.* 35 (2021), 101520.
- [14] I. Kim, R.H. Young, R.E. Scully, Leydig cell tumors of the testis: a clinicopathological analysis of 40 cases and review of the literature, *Am. J. Surg. Pathol.* 9 (3) (1985) 177–192.
- [15] M. Azizi, A.M. Aydin, S.K. Cheriyan, C.C. Peyton, M. Montanarella, S.M. Gilbert, et al., Therapeutic strategies for uncommon testis cancer histologies: teratoma with malignant transformation and malignant testicular sex cord stromal tumors, *Transl. Androl. Urol.* (2019) S91–S103.
- [16] F. Laclergerie, G. Mouillet, A. Frontczak, L. Balssa, P. Eschwege, C. Saussine, et al., Testicle-sparing surgery versus radical orchiectomy in the management of Leydig cell tumors: results from a multicenter study, *World J. Urol.* 36 (3) (2018) 427–433.

- [17] N. Nicolai, A. Necchi, D. Raggi, D. BIASONI, M. Catanzaro, L. Piva, et al., Clinical outcome in testicular sex cord stromal tumors: testis sparing vs radical orchiectomy and management of advanced disease, *Urology* 85 (2) (2015) 402–406.
- [18] M. Azizi, A.M. Aydin, S.K. Cheriyan, C.C. Peyton, M. Montanarella, S.M. Gilbert, et al., Therapeutic strategies for uncommon testis cancer histologies: teratoma with malignant transformation and malignant testicular sex cord stromal tumors, *Transl. Androl. Urol.* 9 (Suppl 1) (2020) S91–S103.
- [19] M. Kapoor, D.P. Budh, Sex Cord Stromal Testicular Tumor, 2021.
- [20] N. Lai, X. Zeng, M. Li, J. Shu, Leydig cell tumor with lung metastasis diagnosed by lung biopsy, *Int. J. Clin. Exp. Pathol.* 8 (10) (2015) 12972.