Case – Leydig cell hyperplasia: A rare ipsilateral co-occurrence with seminoma highlighting the value of 17-OHP in the evaluation of male infertility

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INTRODUCTION

Leydig cell tumor (LCT), classified as a sex cord stromal tumor, is an extremely rare but benign condition representing only 1-3% of testicular tumors. Patients may present with testicular swelling and varying levels of androgen/estrogen secretion from the tumor, possibly leading to precocious puberty, gynecomastia, decreased libido and male factor infertility.[1] Seminoma is a more common pathology, representing 55-60% of testicular malignancies.[2] However, the ipsilateral co-occurrence of the two is extremely rare, with only five reported cases to-date.[3–7]

KEY MESSAGES

- Leydig cell tumor (LCT) co-occurrence with seminoma is extremely rare.
- Serum 17-OHP is a tool to investigate male factor infertility. Scrotal ultrasound of this patient revealed ill-defined hypoechoic foci in the right testicle; 17-OHP was detectable, suggesting the presence of LCT-secreting testosterone.
- Azoospermia persisted post-orchiectomy, potentially due to the loss of the functional testicle.
- The case highlights the utility of 17-OHP in evaluating male infertility and the rarity of synchronous occurrence of LCT and seminoma.

17-hydroxyprogesterone (17-OHP), an intermediate product in the production of testosterone, has traditionally been utilized to screen and monitor for congenital adrenal hyperplasia.[8] Recently, 17-OHP has gained traction regarding its role in the evaluation of male factor infertility, owing to its ability to be an accurate serum marker of intratesticular testosterone (ITT).[9–11]

Here, we present the case of a 32-year-old male patient with the co-occurrence of LCT and seminoma who initially presented with secondary male factor infertility which was investigated with 17-OHP.

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CASE REPORT

A 32-year-old Caucasian male presented with secondary infertility for two years and was subsequently referred to the Manitoba Men's Health Clinic for further evaluation. The patient had previously fathered three uncomplicated pregnancies with the same partner through natural conception. His partner is a 28-year-old woman who is previously healthy with regular periods. Besides ADHD for which he takes methylphenidate, the patient is previously healthy and denies any concerns with erections, ejaculation, libido or energy levels. He is a non-smoker who consumes alcohol socially (~1-2 drinks/week), denies any other substance use, and works as a field manager for a farm.

Hormonal analysis (Table 1) showed his baseline testosterone level was normal with luteinizing hormone (LH) and follicular-stimulating hormone (FSH) levels suppressed well below reference range. Two consecutive semen analyses revealed normal liquefaction, pH, and volume of semen, however, the patient was found to be azoospermic. With the suppression of pituitary hormones (FSH and LH) and normal testosterone, this suggested the patient may have been using exogenous testosterone, resulting in suppression of the reproductive axis. However, the patient denied supplementing with exogenous testosterone. Furthermore, we measured serum 17-OHP. Based on previous literature, 17-OHP should be undetectable in men taking exogenous testosterone.[9] However, we were able to detect it in this patient with a value of 2.3 nmol/L. Physical examination showed the patient had normal secondary sexual characteristics and gynecomastia was not present. Genitalia examination revealed a normal penile shaft and meatus with palpable bilateral vas deference and nontender testes, with the right testicle being larger and the left being marble sized and atrophic. This size discrepancy was reported to be stable as long as the patient could remember.

The patient was sent for a scrotal ultrasound (Figure 1) to identify a potential source of high intratesticular testosterone and investigate the size discrepancy. Results revealed two ill-defined hypoechoic foci in the right testicle, with one measuring 1 x 0.5 cm anteriorly in the mid-testicle and the other being a smaller 3.5 mm lesion seen posteriorly in the upper testicle with increased colour flow indicating vascularity. Alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) were normal at 2 ug/L and 205 U/L, but beta-human chorionic gonadotropin (beta-hCG) was elevated at 60 IU/L.

Given the findings on ultrasound and an elevated beta-hCG, a right radical inguinal orchiectomy was performed without complications and the specimen was submitted for histopathological examination. Pathological examination confirmed the diagnosis of LCT as well as pure seminoma, graded pT1a (Stage 1) and measuring 1.2 cm at maximal dimension (measured as single tumour nodule as both were contiguous [<2 mm apart]) with involvement of the right rete teste and no other high-risk features. Staging CT scan was normal with no evidence of intra-abdominal or intra-thoracic metastasis and the patient undertook active surveillance. AFP, beta-hCG and LDH were all normal post-operatively at 3 ug/L, <1 IU/L and 196 U/L,

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respectively. The patient was subsequently monitored with reproductive hormones illustrated in Table 2. Unfortunately, semen analyses continue to demonstrate azoospermia.

DISCUSSION

In this case, a patient presented with azoospermia attributable to the excess testosterone secretion by a LCT, leading to suppression of LH and FSH through negative feedback. This case highlights the utility of serum 17-OHP in the evaluation of male infertility, a relatively newer tool that has not been widely adopted. 17-OHP was detectable in this patient, confirming the production of intratesticular testosterone, whereas exogenous testosterone use, which was initially considered as a potential etiology, would result in an undetectable serum 17-OHP.[9]

Upon pathological analysis, it was found the patient additionally had pure seminoma, a rare synchronous occurrence with only six total cases now being reported in the literature. Table 3 summarizes clinical information on all current reported cases of LCT co-occurring with seminoma with the mean age of these patients being 33.5 ± 5.4 years. One patient presented with reduced libido and cryptorchidism due to elevated estrogen levels, one patient presented with unilateral testicular swelling, and our patient presented with secondary infertility and unilateral testicular size discrepancy.

Post-orchiectomy, our patient unfortunately had a marked reduction in testosterone. This is most likely due to the left testicle being atrophic at baseline and with the functional right testicle being removed, testosterone production fell along with a large, appropriate rise in LH and FSH. This is similar to a case of LCT presenting with infertility reported by Hibi et al., where a patient also had a left atrophic testicle and upon removal of the right testicle with LCT, the patient had low testosterone with persistent azoospermia, potentially due to the inability of the atrophic testicle to compensate.[1]

While LCT is typically benign (>90%), a radical inguinal orchiectomy is used as the treatment of choice.[1,5] In all five previous cases of reported seminoma and LCT, this was also used as the treatment of choice with two cases using adjuvant radiotherapy. As for recurrence, some cases of LCT with low malignant potential can recur with metastasis and distinguishing this from seminoma is crucial as they do not typically respond to chemotherapy or radiotherapy.[5] For this reason, Obiorah et al. discussed the utility of immunohistochemistry to confirm histological diagnosis in the case of challenging testicular tumors.

CONCLUSIONS

we report the rare co-occurrence of seminoma and LCT with this being the sixth case in the literature. This was associated with secondary infertility in this patient, and we highlight the utility of 17-OHP in assessing intratesticular testosterone levels, aiding in the diagnosis and management of male factor infertility.

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FIGURES AND TABLES

Figure 1. Testicular ultrasound prior to radical inguinal orchiectomy. (A) Ultrasound of scrotum demonstrating hypoechoic foci in the right testicle. (B) Doppler scrotal ultrasound demonstrating vascular flow within the hypoechoic lesion. No varicocele or hydrocele was identified.

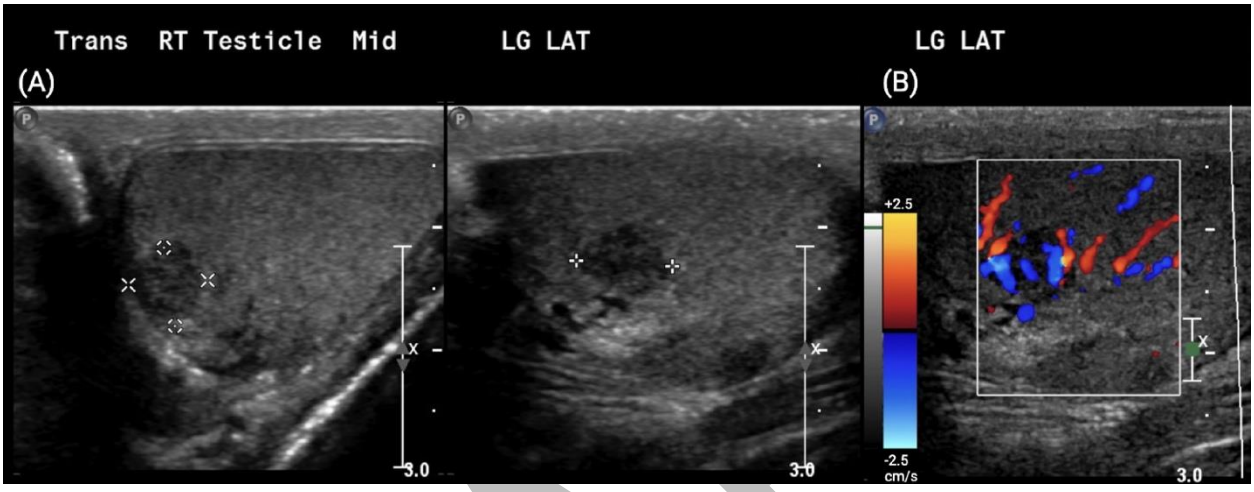

Table 1. Hormonal analysis results at time of presentation. Bold indicates values outside of normal reference range		
Parameter	**Case**	**Normal**
Prolactin (ug/L)	12	0–15
TSH (mU/L)	2.1	0.4–4.2
Luteinizing hormone (IU/L)	**<0.1**	2–18
Follicular-stimulating hormone (IU/L)	**0.1**	1.5–15.0
Testosterone (nmol/L)	24.2	9.7–38
Estradiol (pmol/L)	**277**	0–180
17-OHP (nmol/L)	**2.3**	1.5–6.4

TSH: thyroid-stimulating hormone; 17-OHP: 17-hydroxyprogesterone.

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Table 2. Hormonal analysis two months post right inguinal radical orchiectomy		
Parameter	**Case**	**Normal**
Prolactin (ug/L)	10	0–15
TSH (mU/L)	2.22	0.4–4.2
Luteinizing hormone (IU/L)	**58.8**	2–18
Follicular-stimulating hormone (IU/L)	**126**	1.5–15.0
Testosterone (nmol/L)	**5.9**	9.7–38
Estradiol (pmol/L)	58	0–180

Bold indicates values outside of normal reference range. TSH: thyroid-stimulating hormone; 17-OHP: 17-hydroxyprogesterone.

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Table 3. Summary of reported cases of synchronous Leydig cell tumor and seminoma in an ipsilateral testicle

Case	Year reported	Age	Chief complaint	Associated clinical symptoms	Hormonal abnormalities detected	Laterality	Mass size: seminoma/LCT	Associated GCT	Benign or malignant LCT	Treatment
1[4]	1968	34	NA	None	NA	NA	3.2cm/1.5cm	Seminoma	Benign	Orchiectomy, radiotherapy
2[7]	1979	39	Reduced libido	Cryptorchidism	NA	NA	Total size: 1cm	Seminoma	Benign	Orchiectomy
3[6]	1984	34	NA	None	NA	NA	3.2 cm/1.2 cm	Seminoma	Benign	Orchiectomy, radiotherapy
4[3]	1998	24	NA	None	NA	R	3.5 cm/1 cm	Seminoma, embryonic carcinoma, choriocarcinoma	Benign	Orchiectomy
5[5]	2018	38	Testicular swelling	None	NA	L	6 cm/1 cm	Seminoma	Benign	Orchiectomy
6	2023	32	Secondary Infertility	Larger R testicle size	Suppressed pituitary hormones, high estradiol	R	Total size: 1.2 cm	Seminoma	Benign	Orchiectomy

GCT: germ cell tumor; L: left; LCT: Leydig cell tumor; R: right; NA: not available.

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