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CASE REPORT

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Leydig cell tumor of the testis, presenting with azoospermia

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Abstract

Case: A case of Leydig cell tumor, associated with azoospermia, is presented.

Outcome: The levels of sex hormones obviously were decreased, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH), with elevated testosterone. Computed tomography revealed no adrenal gland tumor, but a significant calcification in the right scrotal content was observed. He received a right radical orchiectomy and then he was unable to ejaculate. An endocrine panel revealed significantly decreased levels of testosterone and the low LH level had remained. Hormone replacement therapy with combined LH and FSH successfully recovered and preserved spermatogenesis.

Conclusions: Although the patient's sexual function deteriorated after surgery, hormone replacement therapy was successful in establishing spermatogenesis.

KEYWORDS

azoospermia, establishing spermatogenesis, hormone replacement therapy, infertility, Leydig cell tumor

1 | INTRODUCTION

Testicular tumors represent 1%-1.5% of all tumors in men. Leydig cell tumors are rare, constituting 1% of testicular tumors. In male adolescents, these hormone-secreting interstitial tumors usually are associated with precocious puberty; the clinical features and hormonal levels of these tumors are varied in adults. Most Leydig cell tumors are benign; however, a radical orchiectomy is currently used as the standard therapy for these tumors. This article presents a case of a Leydig cell tumor that was associated with azoospermia that required hormone replacement therapy after surgery. Moreover, this hormone therapy was successful in establishing spermatogenesis in this patient.

2 | CASE REPORT

A 31 year old male patient was referred to Kyoritsu General Hospital, Nagoya, Japan, owing to azoospermia. Although he had not undergone medical or surgical treatment, he had sustained a scrotal injury from a baseball ball 15 years ago. Azoospermia was confirmed by two semen analyses at the hospital. He was 160 cm tall and weighed 58 kg. His right scrotal content obviously was enlarged and stony-hard in consistency. This enlargement had continued since his scrotal trauma. His left testicle was atrophic (8 mL in volume). His pubic hair was Tanner stage 5 and gynecomastia was absent. The levels of sex hormones, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, free testosterone, and estradiol, were <0.1 mIU/mL, <0.1 mIU/mL, 9.65 ng/mL, 39.5 pg/mL, and 24.8 pg/mL, respectively. The tumor markers of testicular cancer, including alpha-fetoprotein, beta-human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase, were not elevated. The adrenal hormonal levels were almost normal (Table 1) and his blood pressure was 140/90 mmHg. Computed tomography (CT) revealed no adrenal gland tumor and no retroperitoneal and pelvic lymph node swelling, but a significant calcification in the right scrotal content was observed (Figure 1). A chromosomal analysis showed the normal male karyotype of 46,XY and Y chromosomal microdeletion was not detected.

The patient received a right radical orchiectomy for pathological dissection of the tumor under epidural anesthesia with sedation. The resected tissue weighed 236 g and the cut surface revealed a small area of

TABLE 1 Levels of adrenal hormones before surgery

Hormone	6/21/2015	7/2/2015
ACTH (pg/mL)	13.5	12.7
Cortisol (μg/mL)	8.7	6.9
Progesterone (ng/mL)	0.3	0.4
Aldosterone (pg/mL)	234.7	228.3
DHEA-S (ng/mL)	4615.0	4149.0
PRA (ng/mL/h)	3.3	1.7

ACTH, adrenocorticotropic hormone; DHEA-S: dehydroepiandrosterone sulfate; PRA, plasma renin activity.

tumor with obvious calcification (Figure 2). Microscopically, the tumor showed a solid, sheet-like growth pattern and the tumor cells had a large acidophilic cytoplasm with well-defined borders (Figure 3A). Lipofuscin pigments were present in the cytoplasm, while Reinke crystalloids were not identified. Calcification and adipose differentiation were widely observed within the tumor (Figure 3B). Immunohistochemically, the tumor cells were positive for inhibin-alpha and Melan-A (Figure 3C,D). The pathological diagnosis was a Leydig cell tumor.

One month after surgery, the patient was unable to ejaculate and presented with erectile dysfunction and a decreased libido. An endocrine panel revealed significantly decreased levels of testosterone and the low LH level had remained (Table 2).

Two months after surgery, the patient was put on self-administered subcutaneous injections of 5000 units of hCG three times per week for 2 months and this regimen was continued thereafter. Although his sexual function recovered, a semen analysis revealed azoospermia. Additionally, he received subcutaneous injections of 150 units of recombinant human follicle-stimulating hormone (rh-FSH) three times per week. After 4 months of hormone replacement therapy, he was able to produce sperm. His sexual function and spermatogenesis have been maintained for 10 months (Table 3). Unfortunately, his wife could not conceive by natural intercourse.

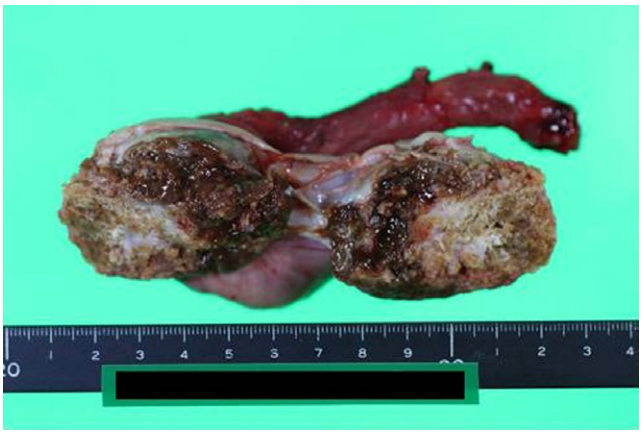

FIGURE 2 Macroscopic findings of the resected right scrotal content. The tissue weighed 236 g and measured 60 mm×50 mm×36 mm in size. Significant calcification was observed

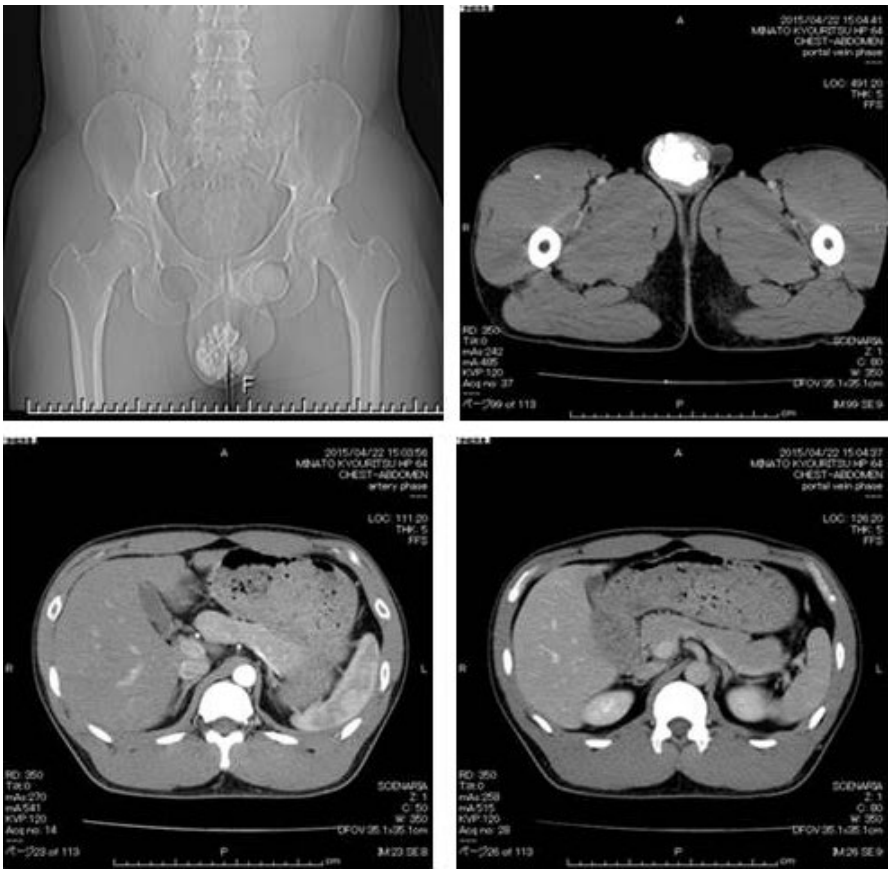

FIGURE 1 Computed tomography scan showed significant calcification in the right scrotal content, with no adrenal gland tumor or retroperitoneal and pelvic lymph node swelling

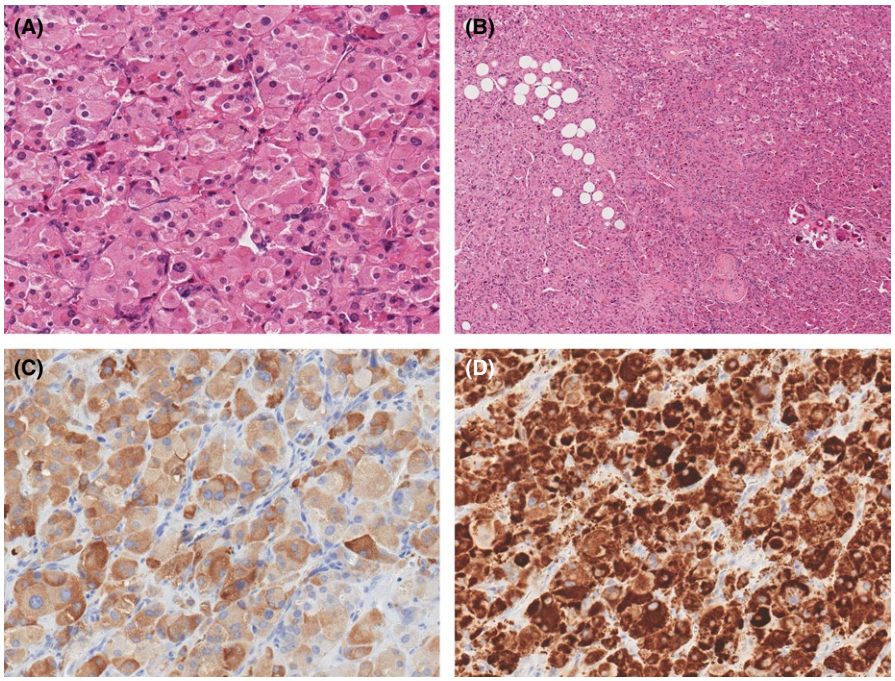

FIGURE 3 Histology of the Leydig cell tumor. A, A solid growth pattern of polygonal cells with abundant acidophilic cytoplasm. B, Adipocyte-like cells and psammomatous calcifications within the tumor. C, Immunohistochemical positivity for inhibin-alpha. D, Immunohistochemical positivity for Melan-A

TABLE 2 Selected sex hormone levels before and after orchiectomy

Hormone	Before the operation (6/21/2015)	1 month after the operation (12/16/2015)	4 months after the operation (3/31/2016)	7 months after the operation (6/25/2016)
Testosterone (ng/dL)	965.0	14.4	218.2	478.4
Free testosterone (pg/mL)	39.5	1.0	4.9	9.3
LH (mIU/mL)	<0.1	0.4	<0.1	<0.1
FSH (mIU/mL)	<0.1	2.5	4.3	4.0
E2 (pg/mL)	24.8	–	–	–

E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

3 | DISCUSSION

Although testicular tumors are uncommon, it is a serious condition for the patient who desires to have offspring. The Leydig cell tumor is very rare, comprising 1%-2% of all testicular tumors, with an ~10% chance of being malignant. Patients with testicular tumors commonly present with asymptomatic scrotal swelling. These tumors show variable endocrinological findings, depending on their ability to secrete steroid hormones. The symptoms include precocious puberty, gynecomastia, decreased libido, and male infertility, such as oligozoospermia or azoospermia.

The height of the patient's father, mother, sister, and brother were 170, 160, 160, and 172 cm, respectively. The onset of puberty occurred when he was ~10 years old and since then he had stopped growing. He was relatively short (height: 160 cm), compared with his family. Although he appeared to have precocious puberty, the adrenocorticotropic hormone level and plasma renin activity were normal. An endocrinologist had diagnosed him with a Leydig cell tumor.

Testosterone is the major hormone that is produced by Leydig cells under feedback control by LH. Testosterone and FSH act directly on the Sertoli cells to promote spermatogenesis. Excess testosterone

TABLE 3 Semen analyses after hormone replacement therapy

Variable	2 months after hCG (3/31/2016)	4 months after hCG/rh-FSH (6/25/2016)	8 months after hCG/rh-FSH (10/25/2016)	12 months after hCG/rh-FSH (2/14/2017)	14 months after hCG/rh-FSH (4/15/2017)
Semen volume (mL)	0.2	1	2	1	1.5
Sperm count ($\times 10^6$/mL)	0	25	32	21	80
Sperm motility (%)	0	52	60	60	31

hCG, human chorionic gonadotropin; rh-FSH, recombinant human follicle stimulating hormone.

secretion in the testis can cause the suppression of LH secretion and induce impaired spermatogenesis.

The marked suppression of LH and FSH and elevated testosterone were associated with azoospermia in this case. An excess testosterone secretion from the Leydig cell tumor might have caused the suppression of LH and FSH. Although the testosterone level was obviously low, the LH level did not recover after the right orchiectomy. The patient's left testis was atrophic in size and his sexual function had significantly deteriorated.

The patient self-injected hCG for 2 months and continued thereafter. Although he recovered his sexual function, a semen analysis revealed persistent azoospermia. In addition to hCG, he was put on rh-FSH. After 4 months of hormone replacement therapy, his sexual function and spermatogenesis were successfully recovered and preserved. Unfortunately, his wife could not conceive by natural means. Moreover, his wife did not hope to receive fertility treatments, such as intrauterine insemination or assisted reproductive technology.

Although most Leydig cell tumors are benign, a radical orchiectomy is currently used as the treatment of choice. With small tumors, testis-sparing surgery is recommended because of the excellent oncological outcome.[1] Tumor enucleation also has been performed with synchronous testicular sperm extraction (TESE) from a macroscopically normal testis. Although sperm motility was achieved, the wife could not conceive.[2,3]

Recently, an article reported a case of unilateral orchiectomy with synchronous TESE in a patient with elevated delta 4 androstenedione and suppressed LH and FSH.[4] Fortunately, the couple achieved a natural pregnancy because of spermatogenesis recovery after surgery. As surgical resection is considered to result in the normalization of gonadotropins and a decrease in delta 4 androstenedione levels, it was hypothesized that this might have induced the spermatogenesis.

Despite the favorable outcome of one patient 4 years after his orchietomy, elevated estradiol and retroperitoneal lymph node swellings were observed.[5] Another study also reported a patient who presented with a hormone-secreting interstitial tumor of the testis and who developed metastasis 7 years after the removal of a benign primary tumor.[6] Therefore, the need for prudential follow-up by CT scans and serum endocrinological assessments was emphasized. Malignant features are characterized as infiltrations of the margins, necrosis, angiolymphatic invasion, and high mitotic figures. However, the only true findings of malignancy have been defined as metastases. Thus, the diagnosis of a malignant Leydig cell tumor is not always easy because no definite histological criteria exist to define malignancy. The panel of antibodies, including Ki-67, p53, and bcl-2, used for immunohistochemical analysis, might have a diagnostic value in the identification of malignant and borderline cases of Leydig cell tumors.[7,8]

In conclusion, Leydig cell tumors are rare and show variable endocrinological findings, depending on their ability to secrete steroid hormones. In the present case, the Leydig cell tumor was associated with azoospermia. Although the patient's sexual function deteriorated after surgery, hormone replacement therapy with combined LH and FSH successfully recovered and preserved spermatogenesis. Regular check-ups with a CT scan is a mandatory requirement in order to detect the possibility of malignancy with recurrence and metastasis.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: All the procedures that were followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from this patient to be included in this study. This article does not contain any study with animal participants that has been performed by any of the authors.

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