Two tumor types in a unilateral testis in a patient with severe oligozoospermia and a history of cryptorchidism surgery: A case report

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Abstract. Testicular cancer, the most common cancer among young male adults, is associated with infertility. A 38-year-old male patient was admitted to Dokkyo Medical University Saitama Medical Center, Japan, with infertility associated with severe oligozoospermia. Scrotal ultrasonography revealed two distinct tumors in the left testis: A mass with abundant blood flow on the cranial side and a mass with poor blood flow on the caudal side. Additional analysis revealed mild elevation of intact human chorionic gonadotropin (hCG) levels (tumor marker level assessment), high testosterone and low luteinizing hormone and follicle-stimulating hormone levels (hormonal level assessment) and severe oligoasthenozoospermia (semen assessment). The preoperative diagnosis was left-sided testicular cancer and severe oligoasthenozoospermia and the patient underwent left high orchiectomy and oncological testicular sperm extraction. Based on the pathological assessment, the cranial tumor was diagnosed as a seminoma with syncytiotrophoblastic cells, whereas the caudal tumor had only scar tissue with germ cell neoplasia *in situ* in the adjacent parenchyma. Following surgery, intact hCG and hormone levels of the patient were normalized, and the semen parameters (semen volume, sperm density, and motility) improved dramatically. To the best of our knowledge, the present case is the first report of two types of testicular tumor in a unilateral testis in a patient with a history of cryptorchidism surgery. The present case demonstrated that scrotal ultrasonography should be performed in patients with abnormal semen results to rule out testicular tumors.

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Abbreviations: FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; onco-TESE, oncologic testicular sperm extraction; GCNIS, germ cell neoplasia *in situ*

Key words: cryptorchidism, oligozoospermia, seminoma, testosterone, testis, tumor

Introduction

Testicular cancer is the most common type of cancer in men aged 14-44 years; its incidence has increased over the past two decades in Western countries (1). Approximately 50% of patients with testicular cancer are diagnosed with seminoma, whereas the remaining are diagnosed with various types of non-seminoma or mixed testicular germ cell tumors (1). The implementation of cisplatin-based chemotherapy regimens and refinement of surgical procedures have improved the long-term survival. The cure rate in all patients with testicular cancer and those with metastatic disease is >95 and 90%, respectively (2). Undescended testis, contralateral testicular tumor, and familial testis cancer are established risk factors for testicular cancer (3). Moreover, there is a proven correlation between infertility and testicular cancer, and infertile men with semen abnormalities are 20 times more likely to develop testicular cancer (4). Future fertility is a concern for young patients undergoing cancer treatment (5). Oligozoospermia is present in >50% of patients with testicular tumors before treatment (6) and testicular tumors are sometimes identified during infertility examinations (7). Declining semen quality in testicular cancer could be due to mechanical loss of physical testicular volume in the affected testis, paracrine and endocrine effects on the ipsilateral and contralateral testis from the tumor, and congenital factors (5).

The present report describes a case in which a patient with infertility and history of cryptorchidism surgery was diagnosed with two types of testicular tumor in one testis; semen parameters and hormonal status improved following high orchiectomy.

Case study

A 38-year-old male patient was referred to Dokkyo Medical University Saitama Medical Center, Saitama, Japan) in April 2021 with oligozoospermia, detected during investigation of infertility. The patient had a history of surgery for left cryptorchidism during infancy and no medication history. A physical examination revealed no abnormalities in the testes. Scrotal color Doppler ultrasonography showed that the right testis was normal; however, the left testis had a mass with clear margins and abundant blood flow in the cranial part and a mass with clear margins but poor blood flow in the caudal part (Fig. 1). Magnetic resonance imaging showed diffusion limitation in the cranial, but not the caudal part, of the left testis (Fig. 2). Chest-abdomen-pelvis computed tomography (CT; TSX-301C/3A, Canon Medical Systems) did not reveal any metastasis.

Tumor marker assessment revealed mildly elevated levels of intact human chorionic gonadotropin (hCG; 29.6 mIU/ml) and normal levels of lactate dehydrogenase (137 IU/l), α-fetoprotein (3.0 ng/ml) and hCG-β (0.1 ng/ml). Hormonal level assessment demonstrated high testosterone (24.69 ng/ml) and estradiol (115.5 pg/ml) levels and low luteinizing hormone (LH; <0.1 mIU/ml) and follicle-stimulating hormone (FSH; <0.1 mIU/ml) levels. Semen analysis was performed according to the WHO 2010 manual (8). Semen analysis revealed severe oligoasthenozoospermia (semen volume, 2.8 ml; sperm density, $0.1x10^6$ sperm/ml; 15 motile sperm were observed in all fields; Table I).

The preoperative diagnosis was left testicular cancer and severe oligoasthenozoospermia. The patient underwent left high orchiectomy and oncological testicular sperm extraction (onco-TESE). Gross examination of the extracted left testis revealed a reddish-brown mass in the cranial and a grayish-white mass in the caudal part (Fig. 3). Pathological assessment was performed on the formalin-fixed, paraffin-embedded (FFPE) tissue block of surgical specimen stained with hematoxylin and eosin. Immunohistochemical staining for octamer binding transcription factor (OCT)-3/4, D2-40, hCG, SALL4 and testosterone was performed on the FFPE tissue block. Samples were fixed in 10% neutral PBS at room temperature for 24 to 48 h; thickness of section, 4 μm. Antigen retrieval was performed using EnVision FLEX Target Retrieval Solution, High pH (Agilent Technologies, 97˚C, 20 min). Quenching step was performed using EnVision FLEX peroxidase blocking reagent, Hydrogen peroxide solution (ready to use, Agilent Technologies); v) the following primary antibodies were used: OCT-3/4 (1:100, NCL-L-OCT3/4, Leica Biosystems), D2-40 (ready to use, 713451, Nichirei Biosciences), hCG (ready to use, IS508, Dako), SALL4 (1:1,000, H6271-6E3, Sigma-Aldrich), and testosterone (1:400, cat. no. ab217912, Abcam) incubated at room temperature for 30 min; vi) the following secondary antibodies were used: EnVision FLEX/HRP (ready to use, K8000, Agilent Technologies), incubated at room temperature for 20 min; vii) EnVision FLEX DAB+ Substrate Chromogen System (Agilent Technologies) was used for chromogen detection, while Mayer's Hematoxylin Solution (room temperature, 30 sec) was used for counterstain. Pathological assessment of the cranial tumor demonstrated a proliferation of tumor cells with round nuclei and well-defined nucleoli. The tumor cells were OCT-3/4$^+$ and D2-40$^+$, and had characteristics of a seminoma with numerous hCG$^+$ trophoblastic cells. The caudal tumor was composed of vitrified material with few cellular components and no evidence of malignancy. Dysplastic cells with round nuclei and well-defined nucleoli were observed in the adjacent intratubular parenchyma. The dysplastic cells were OCT-3/4$^+$ and SALL4$^+$ and had the characteristics of germ cell neoplasia *in situ* (GCNIS; Fig. 4). Both tumors were negative for testosterone. The pathological findings of onco-TESE were a small number of spermatocytes and spermatozoa in a few seminiferous tubules (Johnsen score, 5.4) (9). Based on the pathology, cranial tumor was diagnosed as a seminoma with syncytiotrophoblast cells, and the caudal tumor was diagnosed as regressed GC tumor.

Following surgery, the patient was followed up without medication. At 1 month post-surgery, hormone level assessment demonstrated improvements in several hormone levels (testosterone, 5.24 ng/ml; estradiol, 10.5 pg/ml; LH, 6.5 mIU/ml and FSH, 5.6 mIU/ml). Furthermore, the intact hCG at 10 months after surgery was almost undetectable (<0.5 mIU/ml). Semen analysis 2 months after surgery demonstrated an improvement in semen parameters (semen volume, 5.0 ml; sperm density, $29x10^6$ sperm/ml and motility, 44.8%). The patient and his partner achieved spontaneous conception 12 months after surgery and a healthy baby was born 22 months post-surgery. As of November 2023, the patient had no recurrence at CT follow-up checks and no elevation of serum tumor marker levels 30 months after surgery.

Discussion

The risk of testicular tumor is 4.8-fold higher in patients with a history of cryptorchidism, which is an established risk factor for testicular tumors (3); however, the mechanism underlying the association between cryptorchidism and testicular tumors remains unclear (10). In the present case, two distinct tumors were noted in the left testis of a patient with a history of cryptorchidism, suggesting that cryptorchidism may be associated with tumor development.

Patients with testicular tumors in one testis are more likely to develop contralateral testicular tumors than patients without testicular tumors (3). There are numerous reports of bilateral testicular tumor development (3,11), but no reports of two types of testicular tumors in one testis, to the best of our knowledge. Therefore, the present case is rare.

In the present case, the tumor on the caudal side had regressed, resulting in a lack of symptoms. Hence, it is possible that the tumor on the cranial side (the seminoma) would not have been detected until it increased in size. Early detection was achieved via scrotal ultrasonography during an infertility examination. As certain patients may have no symptoms, scrotal ultrasonography should be performed in those with abnormal semen results to rule out testicular tumors. The cranial seminoma may be considered a metastatic lesion of the caudal tumor and the caudal tumor, which had only scar tissue, may be considered a regressed GC tumor. Pathological findings of regressed GC tumors typically include scarring, decreased spermatogenesis and microlithiasis (12). Notably, the findings of GCNIS in the adjacent parenchyma, and coarse and large intratubular calcifications have been suggested to be

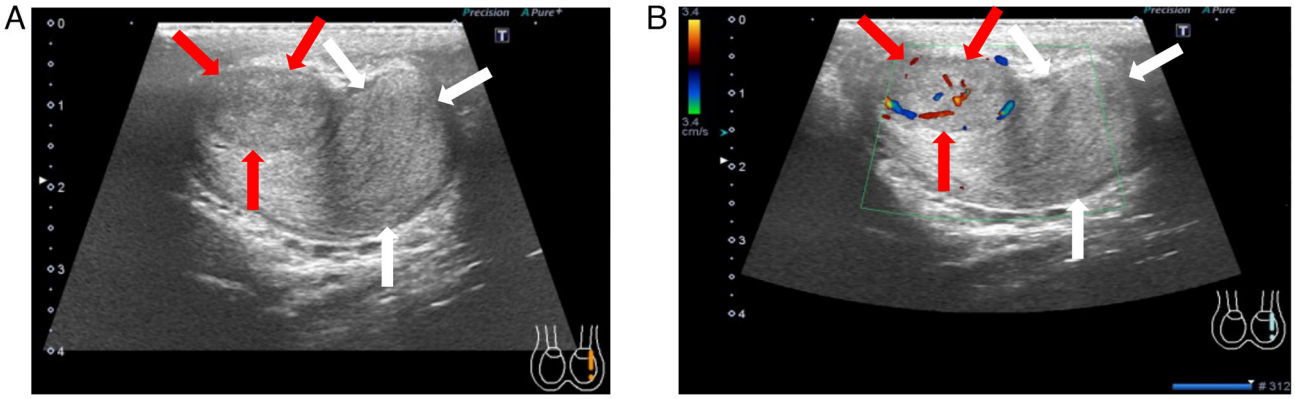

Figure 1. Preoperative ultrasonography of the left testis. (A) Ultrasonographic image shows an isoechoic mass with clear margins in the cranial part and an isoechoic mass with clear margins in the caudal part. (B) Color Doppler ultrasonographic image shows abundant blood flow in the cranial and poor blood flow in the caudal mass. The red and white arrows indicate the cranial mass and caudal mass, respectively.

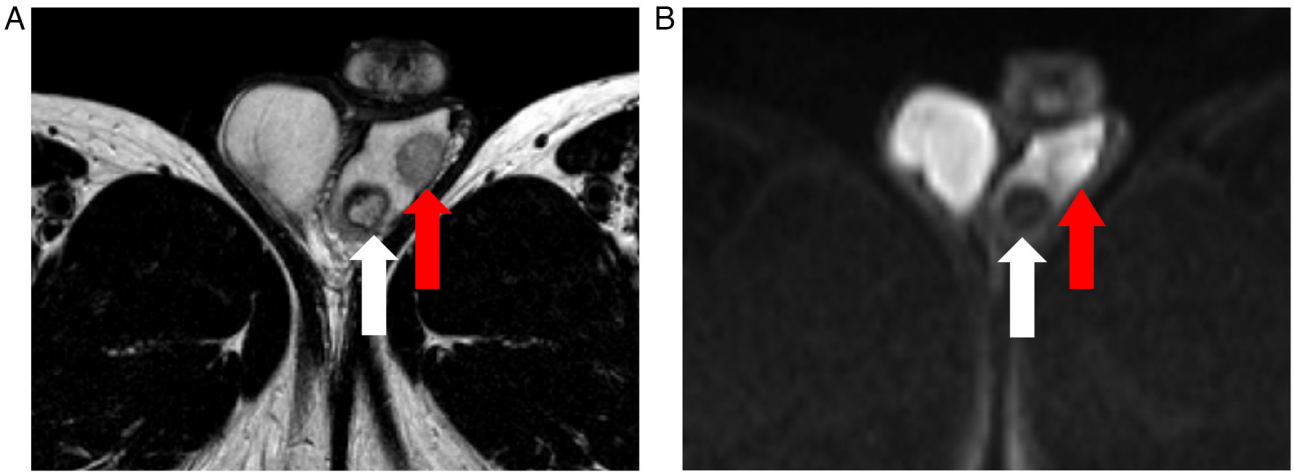

Figure 2. Preoperative magnetic resonance imaging of the left testis. (A) Magnetic resonance image of two tumors at T2 in the left testis. (B) Diffusion-weighted image shows hyperintensity in the cranial and hypointensity in the caudal part. The red and white arrows indicate the cranial tumor and caudal tumor, respectively.

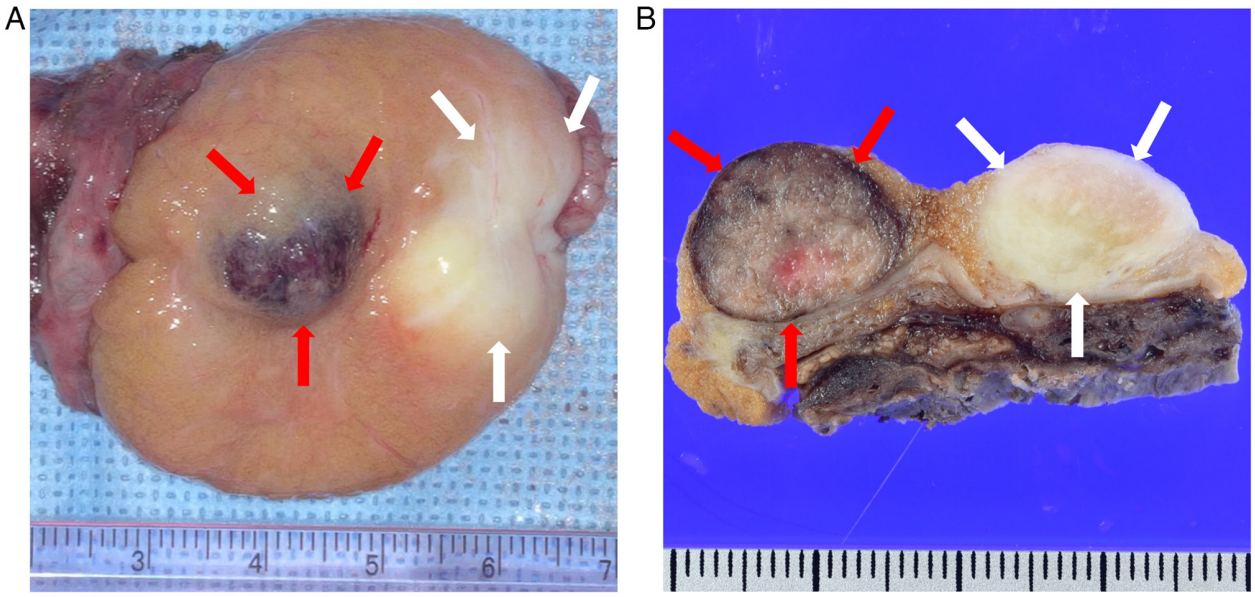

Figure 3. Intraoperative and gross examination findings. (A) Intraoperative image of left testis and (B) cross-section of the formalin-fixed left testis show a reddish-brown mass in the cranial and a grayish-white mass in the caudal part. The red and white arrows indicate the cranial tumor and caudal tumor, respectively.

Table I. Pre- and post-surgery blood and semen parameters.

Value	Pre-surgery	Post-surgery	Reference value	(Refs.)
LDH, IU/l	137	114	124-222	[a]
AFP, ng/ml	3.0	2.9	<10.0	[a]
hCG-β, ng/ml	0.1	<0.1	<0.1	[a]
Intact hCG, mIU/ml	29.6	<0.5	<5.0	[a]
Testosterone, ng/ml	24.69	5.24	1.32-8.71	[a]
Estradiol, pg/ml	115.5	10.5	14.6-48.8	[a]
LH, mIU/ml	<0.1	6.5	2.2-8.4	[a]
FSH, mIU/ml	<0.1	5.6	1.8-12.0	[a]
Semen volume, ml	2.8	5.0	≥1.4	20
Sperm density, $x10^6$/ml	0.1	29.0	≥16.0	20
Motility, %	<0.1	44.8	≥42.0	20

LDH, lactate dehydrogenase; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; [a]Reference intervals were set by the Department of Clinical Laboratory at Dokkyo Medical University Saitama Medical Center.

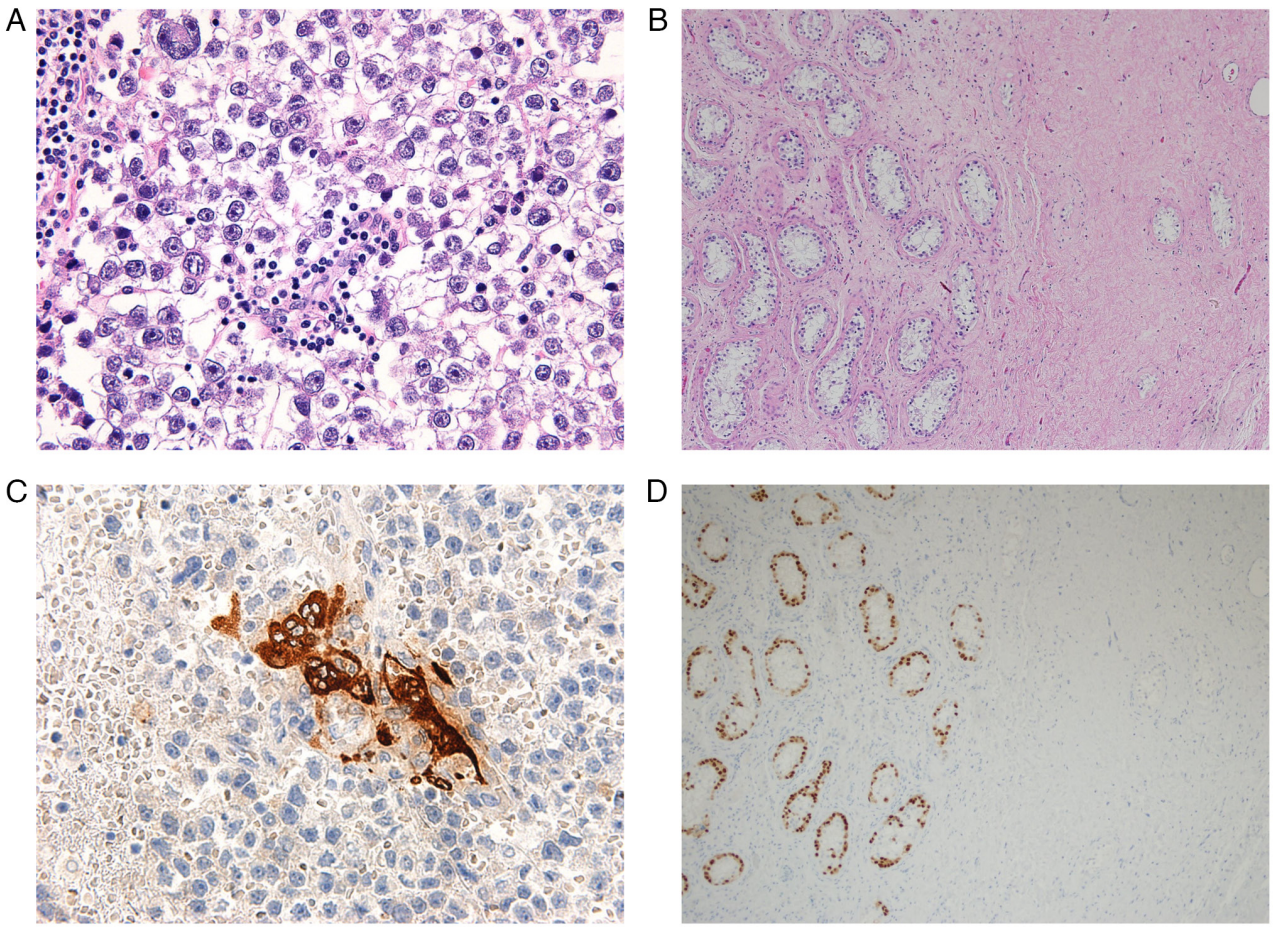

Figure 4. Pathological assessment. (A) Hematoxylin and eosin staining of left testis indicated substantial growth of tumor cells with round nuclei and well-defined nucleoli in the cranial tumor (magnification, x400). (B) Vitrified material with few cellular components and no malignancy in caudal tumor or dysplastic cells with round nuclei and well-defined nucleoli in the adjacent parenchyma (magnification, x100). (C) Immunohistochemical assessment indicated numerous human chorionic gonadotropin-positive trophoblastic cells in cranial tumor (magnification, x400) and (D) octamer binding transcription factor-3/4-positive cells in parenchyma near the caudal tumor (magnification, x100).

specific for GC tumor regression rather than non-neoplastic scarring (12). Non-neoplastic scarring secondary to ischemia, trauma or infection is typically seen in testes lacking diffuse atrophy and is often multifocal. Additionally, non-neoplastic scarring may be associated with vascular lesions such as thrombi and vasculitis and is not associated with more specific

features of regression such as GCNIS, and coarse and large intratubular calcifications. Nodular and stellate atrophy with interstitial fibrosis in testicular regressed GC tumors are distinguished from pure atrophy (13). The patient in the present case had a distinct nodular scar with GCNIS in the adjacent parenchyma, which may indicate a regressed GC tumor.

The association between male infertility and testicular tumors is well-established, and ≤50% of patients with testicular tumors prior to high orchiectomy have abnormal semen parameters (4,14). In the present case, hormonal status (high testosterone and low LH and FSH levels) and semen parameters improved notably following resection of the testicular tumors. This indicated that the testicular tumors caused hormonal abnormalities and infertility. Pathological findings demonstrated no testosterone production in either tumor; however, the seminoma contained syncytiotrophoblast cells that were positive for hCG.

Previous studies have reported that in patients with testicular tumors and elevated blood β-hCG levels, hCG has an LH-like effect, gonadotropin production is suppressed and blood testosterone and estradiol levels are increased (15,16). In the present case, the blood hCG-β levels were within the normal range; however, the intact hCG levels in the blood were mildly elevated, which may have contributed to the increase in testosterone levels. It is likely that hCG concentrations were higher in the left testis than in the blood as hCG is produced by the cranial tumor, a seminoma with syncytiotrophoblast cells (17). The high hCG environment in the left testis may have stimulated the production of testosterone by Leydig cells, which in turn suppressed LH and FSH secretion by the pituitary gland via negative feedback. As a result, spermatogenesis may have been notably inhibited, causing severe oligoasthenozoospermia. In addition, an increase in blood estradiol levels has a negative feedback effect on activity of the hypothalamic-pituitary-gonadal axis (18). In the present case, the estradiol levels were elevated, and suppression of gonadotropin production may have led to progressive dysfunction of spermatogenesis. Testicular tumors promote production of several hormones (e.g., hCG-β, estradiol, and prolactin) and cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor-α) that notably change the intratesticular environment (19). These changes cause spermatogenic dysfunction. The present case is a good clinical example of changes in multiple hormone levels due to testicular tumor treatment improving semen parameters.

In conclusion, the present report describes the first case, to the best of our knowledge, in which two types of testicular tumors were found in a unilateral testis in a patient with a history of cryptorchidism surgery. The present report demonstrated that scrotal ultrasonography should be performed in patients with abnormal semen results to rule out testicular tumors.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

HT, KU, AO and TI participated in the conception, design and data acquisition of the study. HT wrote the manuscript. AF and SB performed the histological assessment of the testis and wrote the manuscript. KU, HO and KS interpreted data and reviewed and edited the manuscript. HT and KU confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was reviewed in accordance with the Dokkyo Medical University Saitama Medical Center Ethics Committee's regulations and approved by the Committee (Koshigaya, Japan; approval no. 22096).

Patient consent for publication

Written informed consent was obtained from the patient for publication of data and images in the present report.

Competing interests

The authors declare that they have no competing interests.

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