Case Report

Testicular seminoma arising from infertile testes 6 years after microdissection testicular sperm extraction

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Abbreviations & Acronyms
CT = computed tomography
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GCNIS = germ cell neoplasia in situ
HE = Hematoxylin and eosin
micro-TESE = microdissection testicular sperm extraction
PLAP = placental alkaline phosphatase
TGCT = testicular germ cell tumor
α-AFP = α-fetoprotein

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Introduction: In Western countries, the risk of a testicular germ cell tumor in men with male factor infertility is greater than in the general population. However, Japanese data on this risk are lacking. Additionally, the clinical course for the pathogenesis involved has not been clearly characterized.
Case presentation: A 35-year-old Japanese male underwent a right orchiectomy because of a mass in his right scrotum. He had a previous history of microdissection testicular sperm extraction undertaken 6 years ago. The final diagnosis of the right scrotal mass was a stage I seminoma. However, a relapse occurred in the left inguinal lymph node 2 years after surgery and the patient was consequently treated with systemic chemotherapy. Pathological analysis of a microdissection testicular sperm extraction sample yielded a germ cell neoplasia in situ in the right testis.
Conclusion: In Japan, men who seek an evaluation for infertility might be more likely to develop testicular germ cell tumor.

Key words: GCNIS, germ cell tumor, infertile testis.

Keynote message

Men who seek an evaluation for infertility might be more likely to develop TGCT. A follow-up study recognizing GCNIS in specimens obtained by micro-TESE should be performed.

Introduction

In Western countries, an increased risk of testicular cancer is observed in men with male factor infertility compared with the general population, but data on this risk in Asian countries, including Japan, are lacking. We here report the case of a patient with a TGCT who underwent a right orchiectomy and systemic chemotherapy 6 years after a micro-TESE for male infertility. We also performed an immunohistochemical analysis of specimens from bilateral testes samples obtained in micro-TESE.

Case report

A 35-year-old Asian male presented at our institution with right asymptomatic scrotal enlargement. His past medical history was bilateral orchidopexy because of bilateral cryptorchidism at the age of 3 years old, and micro-TESE was performed at our institution because of nonobstructive azoospermia at the age of 29. Hematological examination showed high level of human chorionic gonadotropin (8.9 ng/mL; normal range <0.1), and normal levels of lactate dehydrogenase, α-AFP. Ultrasonography showed a well-defined mass with a heterogeneous appearance, measuring 76 × 40 × 53 mm, in the right scrotum (Fig. 1a). Abundant blood flow was detected in the tumor on color Doppler imaging (Fig. 1b). Scattered hyperechoic foci were also observed in the bilateral scrota, indicating testicular microlithiasis (Fig. 1a).

Magnetic resonance imaging showed the enlarged right scrotum with mosaic-intensity on T2-weighted images (Fig. 1d,e) and heterogeneous diffusion restriction on diffusion-weighted images (Fig. 1f). CT revealed no sign of metastasis. Therefore, diagnosed as testicular cancer of cT1N0M0, after informed consent, right inguinal orchidectomy was performed. The tumor was well demarcated, homogeneous, solid cream (Fig. 2a). Hematoxylin and eosin staining of the tumor showed many atypical cells with clear cell bodies and prominent nucleoli (Fig. 2c) with immunoreactive positivity for c-kit (Fig. 2d), PLAP (Fig. 2e), and negativity for AFP. Reflecting the testicular microlithiasis designated in US, multiple calcification was observed in the area with no malignant cells (Fig. 2b), and no germ cell was observed in the tubular section. Finally, he was diagnosed as seminoma pT1N0M0, and surveillance without additional treatment was selected. Two years after the operation, a follow-up CT revealed lymphadenopathy in the left inguinal region (Fig. 1g), demonstrating increased ^{18}F-fluorodeoxyglucose on positron emission tomography-CT (Fig. 1h). Pathological findings of the specimen obtained by the lymph node dissection revealed the identical as the previous orchiectomy one (Fig. 2f–h). Therefore, as a lymph node metastasis of seminoma, he was treated with one cycle of bleomycin, etoposide, and cisplatin, and two cycles of etoposide and cisplatin combination chemotherapy. Four years after the treatment, the patient has now been in remission without sign of recurrence (Fig. 1i).

Discussion

A steady increase in the incidence of TGCT has been noted over the past few decades. The reasons for increasing rates are unclear; however, several clinical risk factors have been identified, including cryptorchidism, as in our case, family history, contralateral TGCT, and infertility itself. To date, with regard to the relationships between infertility and TGCT incidence in Western countries, several large cohort studies have demonstrated a 1.6–2.8 times more likelihood of men presenting with infertility issues developing TGCT compared with those without infertility issues.[1,2] In Asian countries

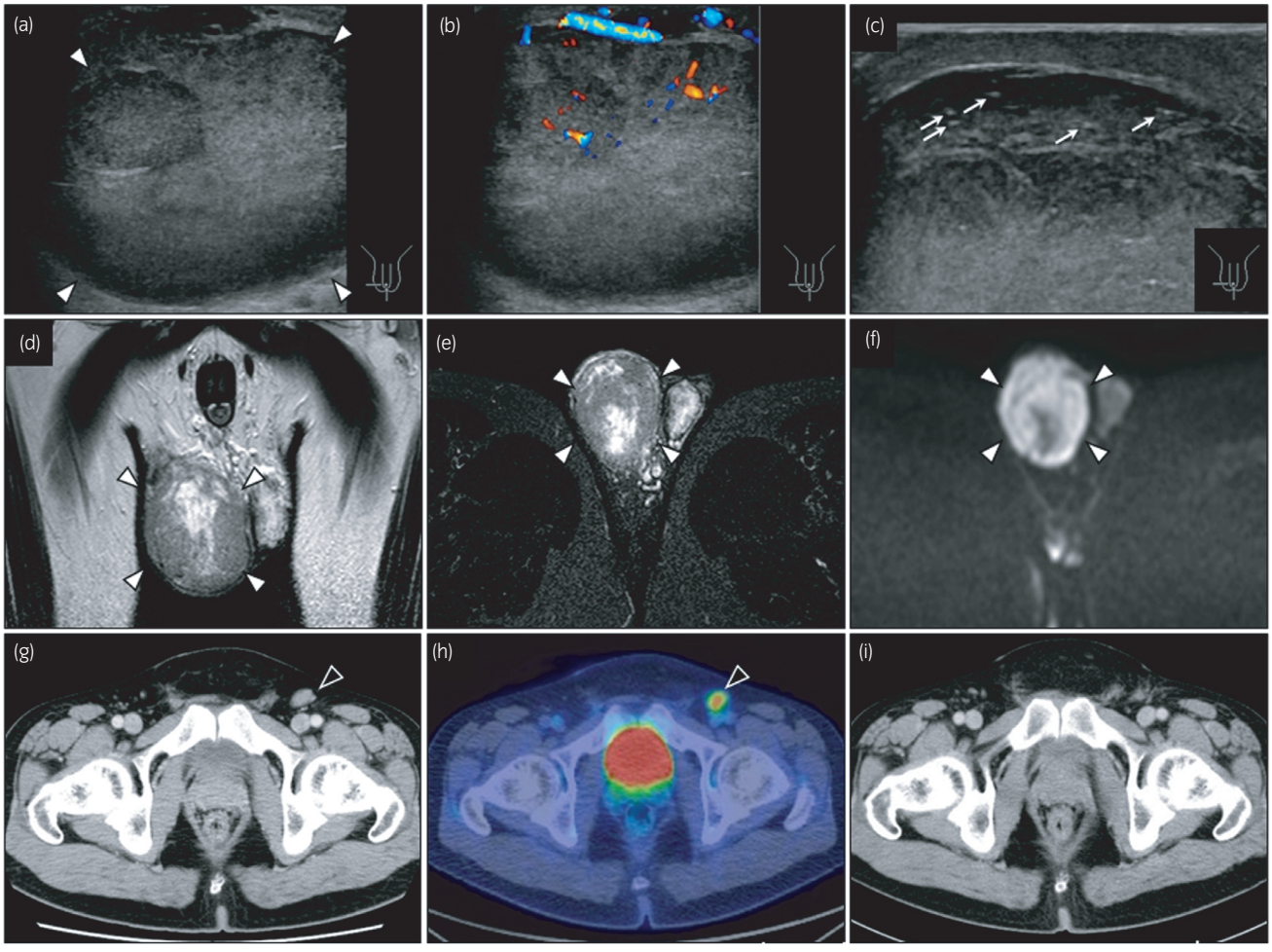

Fig. 1 Ultrasonography shows a well-defined, 76 × 40 × 53 mm mass (white arrowhead) with abundant blood flow in the right scrotum (a and b). Scattered hyperechoic foci (white arrow) are observed in the bilateral scrota, indicating testicular microlithiasis (c). Magnetic resonance imaging shows mosaic-pattern intensity in the enlarged left scrotum on T2-weighted images (d) and fat-saturated T2-weighted images (e). Heterogeneous diffusion restriction is suggested on diffusion-weighted images (f). A follow-up CT performed 2 years after treatment reveals an enlarged left inguinal lymph node (g), demonstrating increased ^{18}F-fluorodeoxyglucose uptake on positron emission tomography (h). There is no sign of recurrence on the following CT 4 years after the second surgery (i).

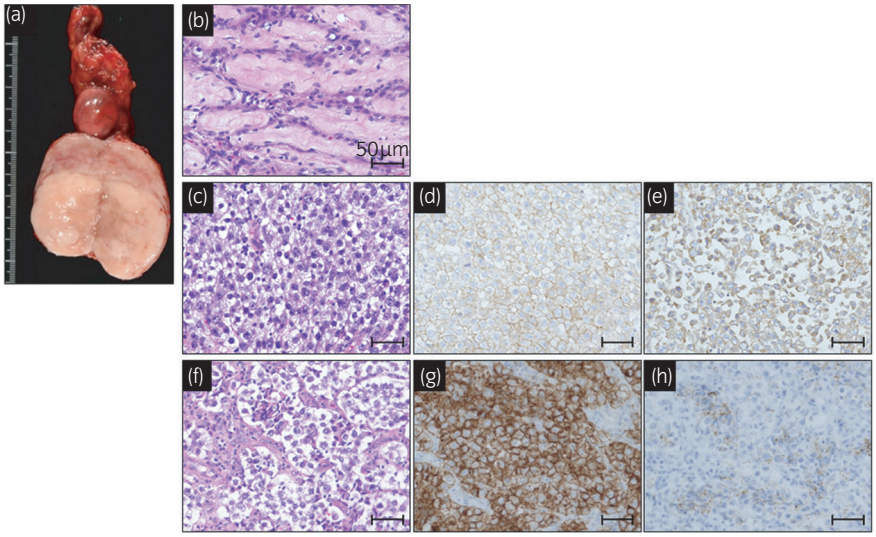

Fig. 2 Macroscopic findings of a right orchidectomy specimen (a). A yellowish mass-like lesion was seen in the testis. HE staining of the tumor showed many atypical cells with clear cell bodies and large nucleoli (c) that stained positive for c-kit (d) and PLAP (e). Hematoxylin and eosin staining of the specimen resected from the inguinal mass revealed this to be identical to a previous testicular tumor (f), being positive for c-kit (g) and PLAP (h).

including Japan, however, evidence based on large data cohorts does not exist with regard to any link between male infertility and TGCT, or the analysis of biology or a precise clinical prognosis. At our institution, from 2004 December to 2018 December, of 1398 male patients who presented to the infertility outpatients department, four patients, including this case, developed testicular tumor, which is a very high incidence compared with the general population, in whom the rate of testicular cancer is 1.30–4.30 per 100 000 males. In the recent Japanese survey of male factor infertility by Yumura *et al*., 17 patients with testicular tumor were found in 7253 patients with male infertility in Japanese article (https://www.yokohama-cu.ac.jp/news/2016/dr3e640000009pzm-att/20160822_h27kourou_yumura.pdf). Therefore, in Japan, men with male factor infertility could be more likely to develop TGCT. In our institution, as shown in Table 1, three of the four patients had stage I seminoma, similar to a previous study.[2] Based on further accumulated real-world data, infertility clinicians should undertake careful palpation and ultrasonography of the testis in patients to ensure the early detection of TGCT, and should ensure the outreach of information on the risk of TGCT to such patients.

In daily clinical practice, when performing micro-TESE, a testicular sample is not generally obtained. However, at our institution, testicular samples are routinely extracted from all patients for the purpose of the pathological evaluation of the grade of infertility after informed consent. Therefore, testicular samples from micro-TESE were immunohistochemically stained. As a result, in hematoxylin and eosin staining (Fig. 3a), gonocyte-like germ cells with a large clear cytoplasm and large angulated nuclei with coarse chromatin clumps were found at the base of seminiferous tubules in the right testis; such cells were positive for c-kit (Fig. 3b) and PLAP (Fig. 3c). However, such cells were not observed in the left testis

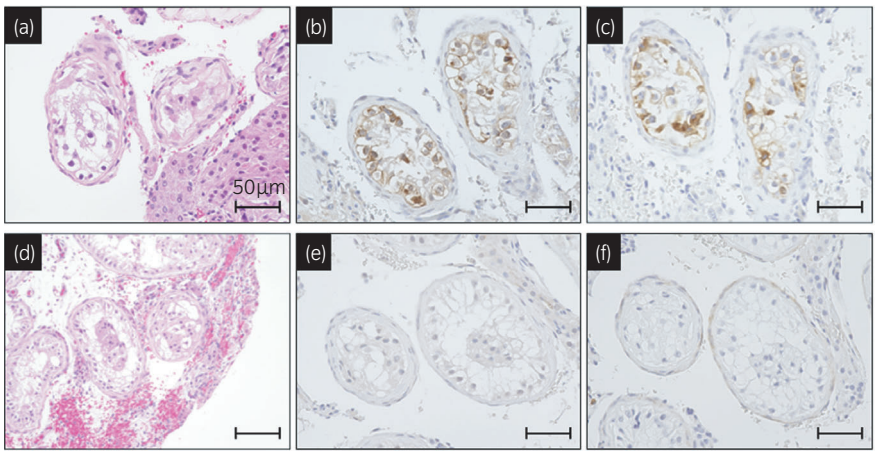

Fig. 3 Pathological analysis using the specimen obtained in micro-TESE. HE (a), c-kit (b), and PLAP staining of the right testis (c). Hematoxylin and eosin staining (d), c-kit (e), and PLAP staining of the left testis (f). Immunostained cells were not observed in the left testis. Micro-TESE, microdissection testicular sperm extraction.

(Fig. 3d–f). These findings suggested the presence of GCNIS that has a distinct histologic pattern preceding the development of seminomatous and non-seminomatous TGCT might have existed only in the right testis when performing the micro-TESE.[3,4] A previous article described how of 534 consecutive male patients with fertility problems who underwent a bilateral testicular biopsy, 13 (2.4%) showed GCNIS.[5] However, a study surveying the proportion of GCNIS that progress to an invasive tumor in patients with infertility is lacking. Considering the clinical course of this case, a follow-up study based on the pathological findings of these rare specimens obtained in micro-TESE has been initiated. It is hoped that the results of this trial will be reported in due course.

Conclusion

In Japan, men who seek an evaluation for infertility may be more likely to develop TGCT. Careful follow-up might be necessary when GCNIS is recognized in specimens of micro-TESE.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the Nagoya City University Graduate School of Medical Sciences Institutional Review Board (#60-19-0234) and it conforms to the provisions of the Declaration of Helsinki.

Informed consent

Written informed consent was obtained from the patient for publication of this article and accompanying images.

Registry and the registration No. of the trial

Not applicable.

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Editorial Comment

Editorial Comment to Testicular seminoma arising from infertile testes 6 years after microdissection testicular sperm extraction

A risk of testicular cancer is increased in men with male factor infertility compared with the general population in western countries.[1] However, data on this risk in Asian countries are lacking. In this case report, Shimizu et al. reported a case report of testicular seminoma arising from right infertile testes 6 years after microdissection testicular sperm extraction (TESE).[2]

In the general population, the rate of testicular cancer is 1.30–4.30 per 100 000 males.[1] In this report, the author showed that 4 of 1398 patients who presented to the infertility outpatients department developed testicular cancer. This finding indicates that the risk of testicular cancer in men with male factor infertility may be increased in Japan. Although further real-world data in Japan are needed, clinicians should pay attention to the risk of testicular cancer when seeing patients with male infertility.

At the author's institute, testicular samples are routinely extracted from patients to evaluate infertility grade when performing micro-TESE. In this case report, immunohistochemistry showed that c-kit and placetal alkaline phosphatase (PLAP) positive cells were found in right testicular samples from micro-TESE. Contrary, such cells were not observed in the left testicular samples. These findings suggest the presence of germ cell neoplasia *in situ* (GCNIS) might have existed in the right testis 6 years before being diagnosed with testicular cancer. Testicular germ cell tumors are the most common solid tumor among adolescent and young adult males.[3] In the future, molecular biological experiments are expected to clarify the mechanism of testicular cancer carcinogenesis.

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