CASE REPORT
https://doi.org/10.5653/cerm.2018.45.1.48
pISSN 2233-8233 · eISSN 2233-8241
Clin Exp Reprod Med 2018;45(1):48-51

CERM

An infertile patient with Y chromosome b1/b3 deletion presenting with congenital bilateral absence of the vas deferens with normal spermatogenesis

Shinnosuke Kuroda[1], Kimitsugu Usui[1], Kohei Mori[1], Kengo Yasuda[1], Takuo Asai[1], Hiroyuki Sanjo[1], Hiroyuki Yakanaka[1], Teppei Takeshima[1], Takashi Kawahara[2], Haruka Hamanoue[3], Yoshitake Kato[1], Yasuhide Miyoshi[2], Hiroji Uemura[2], Akira Iwasaki[1], Yasushi Yumura[1]

[1]Department of Urology, Reproduction Center, Yokohama City University Medical Center, Yokohama; [2]Department of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama; [3]Department of Genetics, Yokohama City University Hospital, Yokohama, Japan

We report the case of a 46-year-old Chinese male patient who visited our clinic complaining of infertility. Semen analysis revealed azoospermia, and azoospermia factor c region partial deletion (b1/b3) was detected using Y chromosome microdeletion analysis. Testicular sperm extraction was performed after genetic counseling. The bilateral ductus deferens and a portion of the epididymis were absent, whereas the remaining epididymis was expanded. Motile intratesticular spermatozoa were successfully extracted from the seminiferous tubule. On histopathology, nearly complete spermatogenesis was confirmed in almost every seminiferous tubule. To our knowledge, this is the first case report of b1/b3 deletion with a congenital bilateral absence of the vas deferens and almost normal spermatogenesis.

Keywords: Male infertility; Y chromosome microdeletion

Introduction

Currently, one in six couples experiences an infertility problem during their reproductive lifetime [1]. Male infertility accounts for infertility in approximately 50% of infertile couples [2,3]. Although there are still many unknown causes of male infertility, chromosomal or genetic abnormalities account for 10% of disorders in spermatogenetic function [4]. The azoospermia factor (AZF) region of the Y chromosome, which is classically divided into the AZFa, AZFb, and AZFc regions, plays an important role in spermatogenesis, and deletions in this region are known to be associated with spermatogenic failure [4,5]. AZF deletion was detected in 10% of infertile men with azoospermia or severe oligozoospermia in a Japanese population [6], but this frequency varies among population groups. Currently, complete deletion of the AZFc region (b2/b4 deletion) is the most common Y-chromosome deletion, and it has never been identified in normospermic men [7]. However, several types of AZFc partial deletions have been identified, including the gr/gr, b2/b3, and b1/b3 subdeletions [8]. There is no consensus on whether partial AZFc deletions affect spermatogenesis, as some authors reported that these deletions are also found in normozoospermic men, with no significant association demonstrated between the deletions and impaired spermatogenesis [9,10]. Among these deletions, gr/gr deletion is most commonly detected. This includes deletion of the azoospermia gene families; some authors reported that gr/gr deletion is a signifi-

Received: Dec 6, 2017 · Revised: Jan 15, 2018 · Accepted: Feb 7, 2018
Corresponding author: **Shinnosuke Kuroda**
Department of Urology, Reproduction Center, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama, Kanagawa, Japan
Tel: +81-045-261-5656 Fax: +81-045-231-1846 E-mail: shinnosuke_1014@yahoo.co.jp

cant risk factor for infertility [8,11,12]. Other groups, however, reported no association between this deletion and spermatogenic failure [13-15]. In contrast, b1/b3 deletion is rare, and its frequency has varied in previous reports [16-19]. Owing to its low frequency, the effects of b1/b3 deletion on spermatogenesis remain unclear [20]. Herein, we present a case of b1/b3 microdeletion with congenital bilateral absence of the vas deferens (CBAVD).

Case report

A 46-year-old Chinese man presented to presented to Reproduction Center of Yokohama City University Medical Center complaining of infertility for 10 years with the following characteristics: testis volume of 12 and 15 mL on the left and right, respectively; not definitively palpable bilateral vas deferens; semen volume of 0.5 mL; azoospermia; normal serum gonadotropin; and luteinizing hormone and follicle-stimulating hormone levels of 9.8 and 10.8 U/mL, respectively. His karyotype was 46,XY. A Y-chromosome microdeletion test showed b1/b3 deletion (AZFc partial deletion). Based on these findings, azoospermia owing to CBAVD or nonobstructive azoospermia due to AZFc partial deletion was suspected. After genetic counseling and obtaining informed consent from the patient and his wife, testicular sperm extraction was performed. The right epididymis body and tail were defective; only the head part was confirmed. The ductus epididymis in the remaining epididymis was expanded, and the vas deferens of both sides was also completely absent. Motile intratesticular spermatozoa were successfully extracted from the seminiferous tubule. On histopathology, spermatogenesis was confirmed, and a few spermatozoa were found in almost every seminiferous tubule. The mean Johnsen score count was 8.3 (Figure 1). The frozen extracted sperm have been used for intracytoplasmic sperm injection (ICSI), which was unsuccessful.

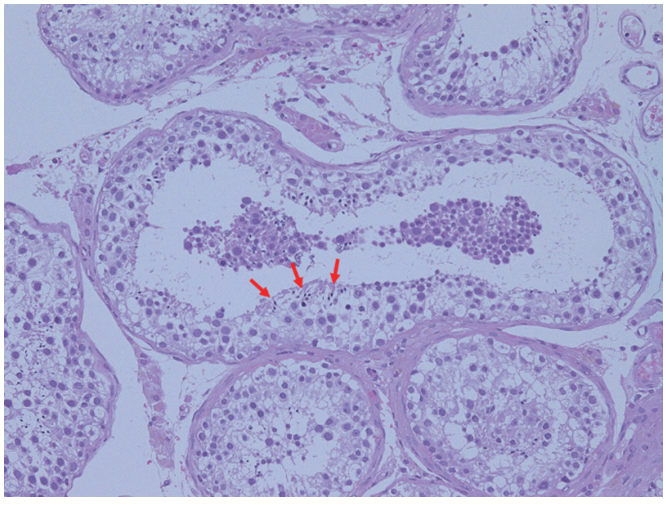

Figure 1. Histopathological findings of the testis (H&E, ×200). Spermatogenesis was confirmed, and a few spermatozoa were found (arrows) in almost every seminiferous tubule. The mean Johnsen score count was 8.3.

Discussion

Y-chromosome microdeletions can be found in 10%–15% of men with azoospermia or severe oligospermia [2]. AZFa region deletions are associated with Sertoli-cell-only syndrome, which is characterized by the total absence of germ cells; however, AZFa deletions are rare. Complete AZFb region deletions are associated with meiotic arrest, which results in azoospermia, whereas complete AZFc deletions are associated with various phenotypes, including oligozoospermia and azoospermia [21]. Therefore, the American Society for Reproductive Medicine states that Y-chromosome analysis and genetic counseling should be offered to men with nonobstructive azoospermia prior to performing ICSI with their sperm, as there is no possibility to extract sperm through testicular sperm extraction when AZFa or AZFb is deleted [22].

The entire length of the AZFc region spans 3.5 Mb, which is removed with the b2/b4 deletion. The b1/b3 deletion removes 1.6 Mb, which is almost half of the AZFc region. This deletion was defined as the loss of sY1161, sY1191, and sY1291 with the presence of other sequence-tagged sites. Repping et al. [8] demonstrated the mechanism of b1/b3 deletion using fluorescence *in situ* hybridization; it occurs through homologous recombination, possibly between sister chromatids or within a chromatid. Since its frequency is very low, the effect of this deletion on spermatogenesis remains unknown. To our knowledge, only 36 cases of b1/b3 deletion have been published in the literature [16,18,19]. Shahid et al. [18] reported 16 patients with b1/b3 deletion, and stated that a statistically significant difference in the frequency of b1/b3 deletion existed between infertile and fertile men ($p = 0.002$). However, Ghorbel et al. [23] reported that b1/b3 deletion was found not only in 13 of 261 infertile men (two with azoospermia, six with oligozoospermia, and five with normozoospermia), but also in three fertile men. In other studies, b1/b3 deletion with normozoospermia was not reported. In our case, testicular histology showed normal spermatogenesis. Thus, if the vas deferens had no defect, this case would be the sixth patient with b1/b3 deletion with normozoospermia.

CBAVD accounts for up to 25% of patients with obstructive azoospermia [24]. CBAVD is sometimes observed as a symptom of cystic fibrosis, a genetic condition causing exocrine gland disorders. Isolated CBAVD is recognized as an autosomal recessive disease that is frequently associated with the cystic fibrosis transmembrane conductance (*CFTR*) gene [25]. According to a meta-analysis of CBAVD, 78%

of patients with CBAVD had at least one *CFTR* mutation, and the 5T allele and 5T/(TG)12_13 may contribute to the increased risk of CBAVD [26]. In our case, a genetic examination for a *CFTR* mutation was not performed because we were not able to do a routine check of the *CFTR* gene in our hospital, and the patient had no past history of chronic bronchitis or sinusitis, which are typical symptoms of cystic fibrosis. In conclusion, we experienced a rare case of an infertile man with b1/b3 deletion. To our knowledge, this is the first case report of a patient with b1/b3 deletion with almost normal spermatogenesis and CBAVD. More cases need to be accumulated for further investigation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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