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LETTER TO THE EDITOR

Male Infertility

Mosaic isodicentric Y chromosome harboring intact AZF region in a cryptozoospermic male with normal hormone levels

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Dear Editor,

Structural aberrations of the Y chromosome, including deletions, ring chromosomes, Y-autosomal or Y-X translocations, isochromosomes, and dicentrics, occur in approximately 0.2% of live births;[1] among these, partial deletion in the azoospermia factor (AZF) region of the Y chromosome is a well-characterized cause of nonobstructive severe oligozoospermia and azoospermia.[2] Meanwhile, a dicentric Y chromosome, abbreviated as dic(Y), was observed to be exclusively present in males with azoospermia, suggesting more severe negative consequences of the AZF deletion for spermatogenesis.[3]

dic(Y), a relatively common Y-linked structural abnormality, which is responsible for nonobstructive azoospermia,[4] greatly impairs the stability of the Y chromosome during cell division. A consequence of this condition is the generation of various somatic cell lines during mitosis, typically including a 45,X cell line.[5] Therefore, most affected patients present with chromosomal mosaicism. Moreover, the formation of dic(Y) mostly results in the loss of Y chromosome-linked AZF,[6] a genomic segment that is indispensable to spermatogenesis. This loss, together with abnormal hormone levels, which are frequently observed in dic(Y) carriers, has been suggested to be the two major causes of nonobstructive azoospermia in males with dic(Y).

The patient was a 33-year-old Chinese male who presented to the outpatient Department of Medical Genetics of the West China Hospital, Sichuan University (Chengdu, China), in September 2019, due to infertility. As required by the Institutional Review Board of West China Hospital (2019 Review No. 783), the patient provided written informed consent for participation in this study. He and his 26-year-old wife had regular and unprotected intercourse in the past 3 years. He had no history of smoking, drug use, or other adverse habits. Seminal examination was conducted three times, and sperm counts were 0–1 per high-power objective (HP). Endocrine tests showed that the level of the follicle-stimulating hormone was 6.6 mIU ml^{-1} (reference value: 1.5–12.4 mIU ml^{-1}) and that of the luteinizing hormone was 4.6 mIU ml^{-1} (reference value: 1.7–8.6 mIU ml^{-1}) and the testosterone level was 4.43 ng ml^{-1} (reference value: 2.49–8.36 ng ml^{-1}). Serum antisperm antibody (AsAb) detection yielded negative results.

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Ultrasound showed that the right testis measured 36 mm × 17 mm × 30 mm (13 ml), with inhomogeneous echo in the parenchymal phase, and the left testis measured 41 mm × 19 mm × 28 mm (15.4 ml), with homogeneous echo in the parenchymal phase. Moreover, ultrasound showed a normal running of the vas deferens and ejaculatory ducts, mild prostate hyperplasia, morphologically normal seminal vesicles, and a normal spermatic vein, without tortuosity or dilatation. Bilateral seminal vesiculography excluded an obstruction of the vas deferens. Further chromosomal G-banding (according to the International System for Human Cytogenetic Nomenclature [ISCN 2016]) of peripheral blood lymphocytes indicated the 45,X[5]/46,XY[25] karyotype (**Supplementary Figure 1** and **2**). Taken together, the patient was diagnosed with idiopathic nonobstructive cryptozoospermia.

To further investigate the submicroscopic variation in the patient's genome, next-generation sequencing was conducted to detect the copy number variant (CNV). The results indicated duplication of a large fragment covering the centromere of the Y chromosome, which was described as [hg19]46,XY,Yp11.31-q11.223 (2616787-24567209) × 2 (duplication span was 21 950.422 kb), in addition to a 405.087-kb deletion at Yq11.23-q12 (28411632-28816719) × 0 (**Supplementary Figure 3** and **4**). An AZF microdeletion test excluded complete deletion of AZFa, AZFb, or AZFc (by analyzing AZFa: sY84, sY86; AZFb: sY127, sY134; and AZFc: sY254, sY255, at the West China hospital, Chengdu, China), and no deletion of any locus was found. Fluorescence *in situ* hybridization (FISH) was performed using sex-determining region on the Y chromosome (Y-SRY; Yp11.3, red), Y-centromeric sequence (Y-DYZ3; Yp11-q11, red), and X-centromeric sequence (X-DXZ1; Xp11-q11, green) probes. The results showed two fluorescent signals of SRY and two signals of DYZ3 on the Y chromosome, suggesting the presence of an isodicentric Y chromosome (**Figure 1a** and **1b**). The FISH karyotype of the patient was eventually described as 45,X/46,X,ish psu idic(Y)(q11.23)(SRY++,DYZ3++).

In the present study, a cryptozoospermic patient was found to have a mosaic of 45,X/46,XY, with 46,XY as a predominant cell line. Superficially, a decrease in the dosage of the Y chromosome seems to negatively influence spermatogenesis. However, it is difficult to confirm the association between the karyotype and severe spermatogenic failure, considering that 83.3% (25/30) of somatic cells contain the Y chromosome. The formation of 45,X/46,XY mosaicism has been associated with a structural variant of the Y chromosome and

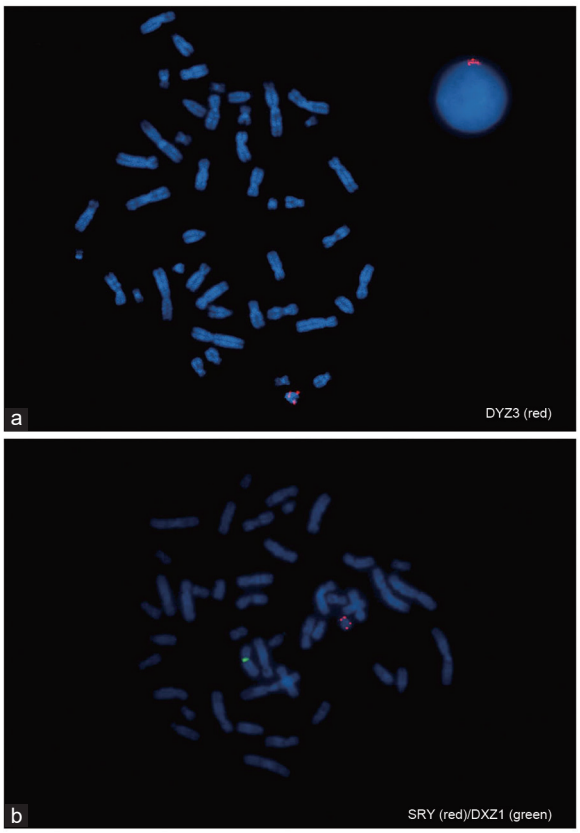

Figure 1: (**a**) FISH results obtained using a DYZ3 probe (indicating that the patient has two Y centromeres). (**b**) FISH results obtained using SRY and DXZ1 probes (indicating that the patient has two short Y arms). FISH: fluorescence *in situ* hybridization; DYZ3: sequence in the centromeric region of chromosome Y; SRY: sex-determining region of Y-chromosome; DXZ1: alpha satellite sequence in the centromeric region of chromosome X.

the resulting mitotic abnormality. Moreover, a structurally mutated Y chromosome in spermatogenic cells usually causes more severe consequences, such as severe spermatogenic failure, which are due to the abnormality of the X-Y exchange and a loss of Y-linked genes during meiosis.[7] Therefore, we suggested further genetic analyses of the patient.

The formation of idic(Y) may occur at Yp or Yq. When it occurs at Yp, patients are highly likely to become anatomically feminized, owing to the disturbance of the SRY region. When the formation of idic(Y) occurs at Yq, patients are highly likely to become azoospermic, owing to the deletion of the AZF region and abnormal hormone levels.[8,9] In this case, the patient was a cryptozoospermic male with an isodicentric Y chromosome harboring an intact AZF region and normal hormone levels. A study has suggested that the intercentromeric distance is correlated with the stability of idic(Y) (the longer the distance is, the more unstable idic(Y) will be).[3] Our case is rare, given that the breakpoint occurred at Yq11.23 (proximal to the telomere), with normal hormone levels. Two studies have reported patients with idic(Y) with similarly long intercentromeric distances, but one of the patients was a male with abnormal hormone levels, and another was a fetus;[8,10] therefore, the correlation between meiosis and spermatogenesis failure cannot be explained by these two cases.

In conclusion, we identified, for the first time, a dic(Y) characteristic of breaking and joining of two Y chromosomes proximal to a telomere (Yq11.23) in a patient with cryptozoospermia. This rare case may provide evidence for the hypothesis that the critical factor causing severe spermatogenic failure in males with dic(Y) may be the disturbance of the process of meiosis due to the dosage and location changes of X-Y exchange targets. However, only one case is not sufficient for a firm conclusion, more data should be collected to confirm this assumption.

AUTHOR CONTRIBUTIONS

YY and SYX designed the study and wrote the manuscript. YY supervised the study. SYX, DCT, and YY analyzed and interpreted the data. SYX collected the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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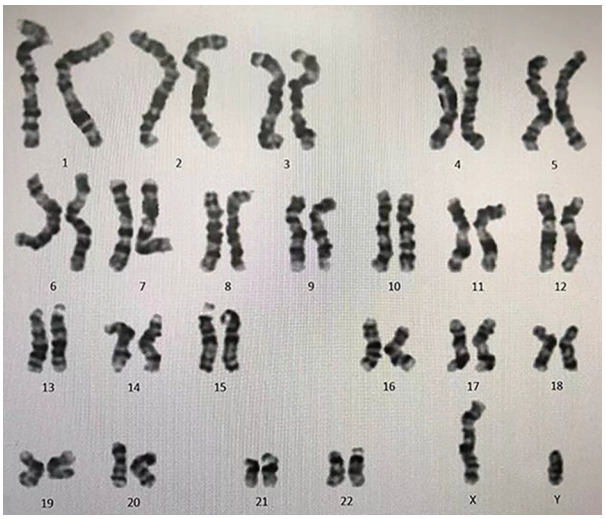
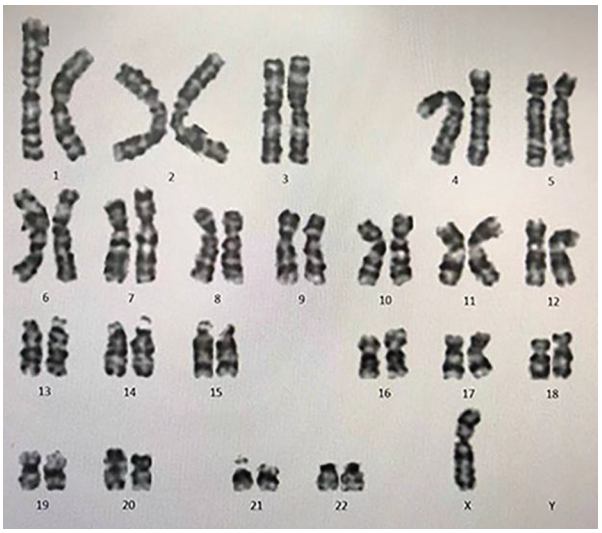
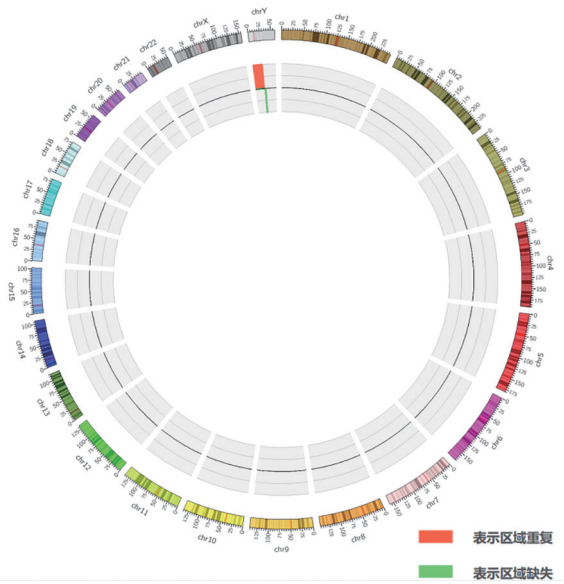


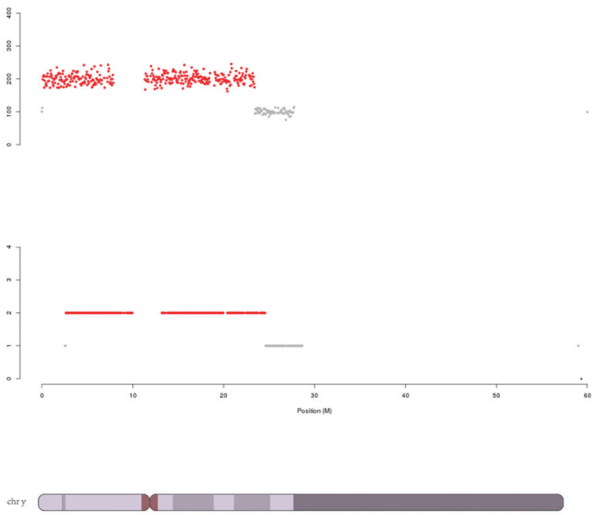
Supplementary Figure 1: G-banding of the patient's chromosomes (pairing of homologous chromosomes [46,XY cell line]).



Supplementary Figure 2: G-banding of the patient's chromosomes (pairing of homologous chromosomes [45,X cell line]).



Supplementary Figure 3: CNV-seq of the patient's chromosomes (the circle at the center: the red region represents duplication, and the green region represents deletion).



Supplementary Figure 4: CNV-seq of the patient's chromosomes (Yp11.31-q11.223 [2616787-24567209] × 2 [duplication span was 21 950.422 kb] and a 405.087 kb deletion at Yq11.23-q12 [28411632-28816719] × 0).