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LETTER TO THE EDITOR

A PATIENT WITH AZOOSPERMIA AND 45,X/46,X,r(Y) (p11.2q11.2) MOSAICISM WITHOUT AZF DELETIONS

BY O. ALTIOK CLARK [1], I. TÜRKER KÖKSAL [2], S. BERKER KARAÜZÜM [3] AND Z. CETIN [4]

Infertility is an important health problem which affects aproximately 10-15% of couples and, in 30-50% of these couples, infertility is due to male factor infertility (1). Recently, Hoffher *et al.* (4) performed a meta-analysis by reviewing previously published reports in the literature to determine the cumulative frequencies of chromosomal abnormalities and chromosome Y microdeletions in infertile males. According to their results, the 47,XXY karyotype, which is associated with both Klinefelter syndrome and its variants, were found to be the most frequent chromosomal abnormalities, with a frequency of 4.9%, followed by autosomal chromosome abnormalities (3.5%) and structural sex chromosomal abnormalities (1.8%). Furthermore, they estimated that the frequency of Y chromosome microdeletions in infertile males was 3.5% (4). To the best of our knowledge, there have been only thirteen cases reported in the literature in which male factor infertility was found in association with a ring Y chromosome, and in only two of these cases was the male factor infertility not associated with loss of AZFa,b,c regions located at Yq11.2. While one of these two cases had oligoasthenospermia, the other had azoospermia.

Here, we describe the second male patient found with azoospermia in conjunction with mosaicism for 45,X karyotype and ring Y chromosome without AZFa,b,and c deletions.

A 29-years old man was admitted to our clinic due to male factor infertility. Neither his previous medical nor family history contained any information of relevance to his case. On physical examination, both testes were soft and 12 cc in size. The ductus deferens was palpable and normal in shape, bilaterally, and there wasn't any sign of varicocele on either side. Analysis of the patient's semen was performed on 2 different occasions and revealed complete azoospermia. The patient's hormone profile was found to be as follows: luteinizing hormone levels were 3.580 mIU/ml (1.70-8.60 mIU/ml), the follicle stimulating

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hormone levels were 2.760 mIU/ml (1.50-12.40 mIU/ml), and total testosterone and free testosterone levels were 2.630 ng/ml (2.80-8.00ng/ml) and 10.050 pg/mL (8.90-42.50 pg/mL), respectively. As is standard procedure with men found to have azoospermia, the patient was referred to the medical genetic diagnostic laboratory for both chromosomal karyotyping and Y chromosome microdeletion analysis.

Conventional cytogenetic analysis of the patient's peripheral blood lymphocytes revealed a ring chromosome Y (Fig. 1a). C-banding showed that ring chromosome Y was monocentric and did not contain a constitutional heterochromatin region located in the Yq12 band (Fig. 1b). Therefore, the breakpoint on the long arm of chromosome Y was thought to be Yq11.2. The karyotype of the father was found to be normal. FISH analysis showed that the SRY located in the Yp11.2 and centromeric alfa satellite DNA was intact on ring chromosome Y (Fig. 1c-d). Based on the FISH analysis, the patient's final karyotype was designated as: 45,X[10]/ 46,X,dic r(Y)(p11.2.q11.2)[4]/ 46,X,r(Y)(p11.2.q11.2)[86]. ish r(Y)(p11.2q11.2) (SRY+, DYZ3+, DYZ1-). Y chromosome microdeletion analysis showed that the patient did not have any genomic deletions in the AZFa, AZFb and AZFc regions on the long arm of the Y chromosome.

There are only six previous reports in the literature of infertile males that had a ring Y chromosome with AZF deletions that had been studied (2, 3, 5, 6) (Table I). As with our case, five of these patients had

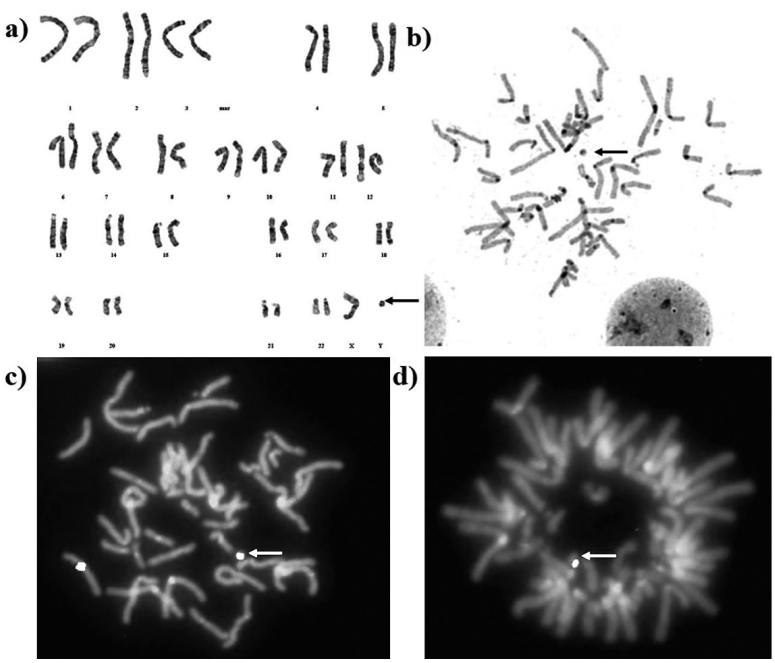

Figure 1:
a) Karyotype of the patient showing a normal chromosome and ring chromosome Y.
b) CBG banded metaphase plate of the patient with a black arrow indicating ring chromosome Y with centromeric heterochromatin.
c) Representative picture from FISH analysis showing that the ring chromosome Y contains DYZ3(Yp11.1q11.1) located in the centromeric region.
d) Representative picture from FISH analysis showing that SRY(Yp11.2) was present on ring chromosome Y, while DYZ1(Yq12) located in the constitutional heterochromatin region was deleted.

Table I: Previously reported cases with ring chromosome Y and azoospermia

Case	Karyotype by GTG Chromosome Analysis	Phenotype	Y Chromosome Deletion Analysis	FISH Analysis	Age (years)	Spermiogram	Reference
1	45,X[26]/46,X,ring(Y)[74]	normal male	NORMAL	WCPY+, DYZ3+, SRY+	32	oligoastenospermia	Layman LC *et al.* (5) (case 5)
2	45,X[9]/46,X,ring(Y)[11]	short stature	AZFa,b,c deletion	Ypter-, Yqter-, DYZ3+	38	azoospermia	Lin YH *et al.* (6) (Case 1)
3	46,X,ring(Y)[20]	normal male	AZFb,c deletion	Ypter-, Yqter-, DYZ3+	40	azoospermia	Lin YH *et al.* (6) (Case 2)
4	45,X[8]/46,X,ring(Y)[92]	normal male	Complete AZFc deletion and partial AZFb deletion	WCPY+, DYZ3+, SRY+, Ypter-, Yqter-,	38	azoospermia	Bertini *et al.* (2) (Case 1)
5	45,X[5]/46,X,ring(Y)[95]	normal male	AZFa,b,c deletion	WCPY+, SRY+, Ypter-, Yqter-	42	azoospermia	Bertini *et al.* (2) (Case 2)
6	46,X,r(Y)(p11.3q12)[68]/45,X [22]/46,X,dicr(Y)(p11.3q12;p11.3q12)[10]	short stature	NORMAL	DAZ+, DYZ3+	35	azoospermia	Dong *et al.* (3)
7	45,X[10]/46,X,dicr(Y)(p11.2.q11.2) [4]/46,X,r(Y)(p11.2.q11.2)[86]	normal male	NORMAL	SRY+, DYZ3+, DYZ1-	29	azoospermia	Present case

NP: Not performed; NR: Not recorded

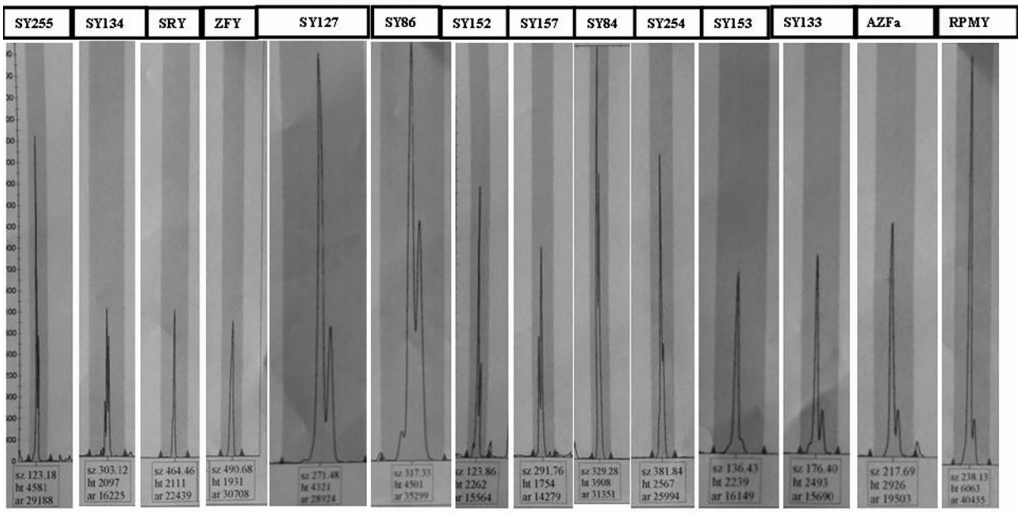

Figure 2:
A representative figure of Y chromosome microdeletion analysis using ZFX/ZFY and SRY control loci and 12 different STS markers in the AZFa,b and c regions (Sy255, Sy134, RBMY, AZFa, Sy133, Sy152, Sy153, Sy157, Sy84, Sy86, Sy127, Sy254), indicating the absence of Y chromosome microdeletions in the AZFa,b and c regions.

azoospermia, whereas one case had oligoastenospermie and the other had oligoastenospermia. Five cases had varying degrees of mosaicism for 45,X and 46,X,r(Y) cell lines. Only one case had 45,X,r(Y) karyotype in a regular state (2;(case 2)). Four cases were phenotypically normal males whereas remaining two cases presented only short stature.

Among the six cases in which Y chromosome microdeletion analysis was performed, Y chromosome microdeletions in the AZFa,b,c regions were detected in four. Only two cases reported by Layman *et al.* (5) (case 5) and by Dong *et al.* (3) had normal results for Y chromosome microdeletion analysis. One of these cases had azoospermia, like our case, while the other had oligoastenospermia. In this study, we performed Y chromosome microdeletion analysis, the results of which ruled out the possibility of AZF deletions in the pathogenesis of the patient's infertility.

As a result, ring Y chromosome without AZF deletions is a rare but recurrent chromosomal abnormality in male factor infertility. The underlying cellular mechanisms are not clearly explained yet, but defective spermatogenesis in some cases with ring Y chromosome is not associated with deletions of the gene or genes at the AZFa,b,c loci on chromosome Y. Still, however, the possibility that currently uncharacterised autosomal genes may have an impact on male factor infertility cannot be ruled out. If couples suffering from male factor infertility decide to undergo assisted reproduction procedures to conceive a child, preimplantation genetic diagnosis should be performed before transferring embryos due to the increased risk of numerical chromosomal abnormalities.

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