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·Letters to the Editor·

45,XY,der(13;14)(q10;q10) in an azoospermic man with hypogonadotrophic hypogonadism

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Dear Sir,

I am Feride Iffet Sahin in Baskent University Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey. We write to you about a case of 45,XY,der(13;14)(q10;q10) in an azoospermic man as a result of hypogonadotrophic hypogonadism.

The most frequent form of Robertsonian translocation is between chromosomes 13 and 14 [1]. It is reported to be a cause of male infertility [2–4]. The frequency of Robertsonian translocation among infertile men has been reported to be 1%, which is higher than that of the normal newborn population [2, 5]. The translocated chromosomes cause inappropriate pairing during male meiosis and hinder normal sperm production, resulting in oligo- and azoospermia.

A 34-year-old male patient was referred to the Department of Medical Genetics from the Department of Obstetrics and Gynecology, Baskent University Faculty of Medicine, for chromosome analysis and Y microdeletion testing because of azoospermia as a result of hypogonadotropic hypogonadism.

During genetic counseling, we learned that the patient was one of the seven children of a nonconsanguineous married couple. The patient's mother had no miscarriages in her obstetric history. All his married siblings (three sisters and three brothers) had healthy children. His two elder sisters each had two spontaneous abortions in their obstetric history. There were no other significant findings in his family history. Cytogenetic and Y-deletion screening tests were performed after informed consent was obtained from the patient.

The diagnosis of hypogonadotrophic hypogonadism was made in the Endocrinology Department of our university by low luteinizing hormone (LH), follicle-stimulating hormone (FSH) and total testosterone levels 4 years ago. The baseline serum concentrations of thyroid-stimulating hormone (1.32 μIU/L, normal range [n.r.]: 0.3–4.0 μIU/L) and prolactin (211.64 mIU/L, n.r.: 25.20–628.53 mIU/L), were normal, but those of FSH, LH and total testosterone were very low in serum samples collected on different occasions (0.19–0.44 mIU/mL, n.r.: 1–15 mIU/mL; 0.07–0.08 mIU/mL, n.r.: 2–10 mIU/L; and 1.70 ng/mL, n.r.: 2.88–8.88 ng/mL, respectively). Blood samples were obtained 0, 25, 75 and 90 min after stimulation with 100 mg intravenous GnRH-a (Leuprolide acetate; Lucrin, Abbott, France) for examination of FSH, LH and total testosterone levels. Extremely low non-pulsatile FSH (1.24, 1.33 and 1.40 mIU/L, respectively) and LH levels (0, 0.22 and 0.12 mIU/L, respectively) were obtained after 0, 25 and 75 min, whereas a rise in total testosterone levels was detected (0.2, 3.57 and 4.11 ng/mL at 0, 75 and 90 min, respectively). It is likely that the pituitary insufficiently prevented the normal rise in se-

rum FSH and LH levels. Inhibin B levels were not obtained because of the condition of our laboratory.

There was no history of episode of anosmia, head injury or granulomatous diseases, such as tuberculosis or excessive exercise. No causative abnormalities were detected in imaging studies, including magnetic resonance imaging of hypophysis and computed tomography of the head. The patient was not married at the time of the present study, and complained of sexual infantilism. His penis was measured at 6 cm and testicles were recorded to be small. Azoospermia was detected in spermiogram. After the diagnosis, he was treated with testosterone and human chorionic gonadotrophin (HCG) preparations for 6 months. Total testosterone levels elevated after this period (7 ng/mL) but azoospermia persisted despite normal testosterone levels. After 6-month treatment, testosterone treatment discontinued and HCG was administered for additional 6 months. After this treatment period, testosterone level was still in the normal range (total testosterone [6.51 ng/mL, n.r.: 2.88–8.88], free testosterone [20 pg/mL, n.r.: 6.2–28.1], FSH [1 mIU/L] and LH [< 0.07 mIU/L] levels remained low and spermiogram revealed 1–2 immotile spermatozoa). Treatment protocol was shifted to Follitropin alpha 150 IU and HCG 1500 IU every other day and the patient was followed for additional 2 years. Although testosterone remained normal, we could not detect any changes in the spermiogram. He was married during the 2-year follow-up and consulted Assisted Reproduction Unit, Department of Obstetrics and Gynecology, for further investigation because of infertility. In the scrotal ultrasonography (USG), bilateral testicular atrophy and varicocoele of the left testis was detected. The spermiogram was reported as azoospermia once more and testis biopsy was performed.

Following the tissue processing, biopsies were embedded in paraffin blocks. Four-μm-thick sections from each specimen were taken and stained with hematoxylin and eosin (HE). Microscopic evaluation of HE stained sections revealed thickening in basement membranes of seminiferous tubuli. Most of the tubuli were composed only of sertoli cells. Few tubuli contained germ cells showing maturation up to the spermatide I–II level. The diagnosis was incomplete maturation arrest.

Chromosome analysis was made from peripheral blood lymphocyte cultures according to standart protocols and Trypsin-Giemsa banding (GTG) at the 450–500 band level was performed. Karyotype analysis was made in 30 metaphase spreads resulting in 45,XY,der (13;14)(q10;q10) (Figure 1) [6].

Genomic DNA was isolated from peripheral blood samples by DNA isolation kit (Roche Diagnostics, Code: 1 796 828, Mannheim, Germany). Microdeletion analysis was carried out using two primers (sY 84 and sY 86) for AZFa, three primers (sY 131, sY 143 and sY 164) for AZFb and five primers (sY 152, sY 254, sY 255, sY 277 and sY 283) for AZFc regions, and polymerase chain reaction (PCR) products were analyzed by running in 2% agarose gels. No deletions were detected.

In the current case, our patient had a Robertsonian translocation involving chromosomes 13 and 14. In the Robertsonian translocations, prophase I of meiosis results in a trivalent structure because of the rearrangement of the chromosomes, and results in alternate segregation. Changed segregation patterns might result in balanced or unbalanced gametes and offspring. Unbalanced offspring are usually lost by spontaneous abortions [7].

Male infertility is associated with structural chromosome abnormalities [3]. Meiotic behavior of translocation chromosomes results in different degrees of meiotic arrest and oligozoospermia or azoospermia are found in these patients [4]. Luciani *et al*. [8] investigated the mechanism of segregation in meiosis in a der(13q;14q) carrier. They tried to elucidate the reason for spermatogenesis arrest in men.

Sex vesicle formation occurs in male pachytene and X and Y chromosomes together are responsible for the structure. No sex vesicle is formed during female meiosis [9]. In XXY males, no sex vesicle formation is observed in cells with an XX bivalent and X-chromosome inactivation cannot occur, which leads to meiotic arrest [3].

In der(13q;14q) patients, a trivalent configuration

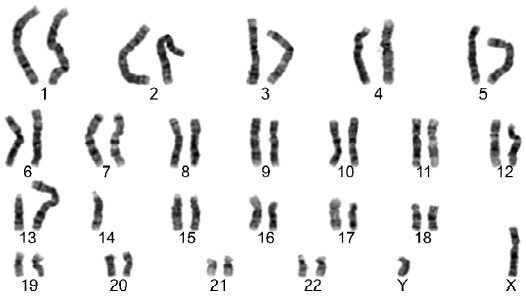

Figure 1. Karyotype of the patient showing the translocation.

occurs in meiosis between the normal and translocation chromosomes. They completely pair from band p11 to the distal long arm. The normal and translocated chromosomes differ in a lightly stained region distal to the short arm. With silver staining methods, the region was heavily stained in normal chromosomes, indicating the nucleolar organizing region (NOR). In translocation chromosomes, the NOR region was not stained. This trivalent interacts with the sex vesicle through the X chromosome, not the Y chromosome [8]. The interacting region is the centromere of the translocation chromosome. The normal chromosomes joining the trivalent structure associate with other acrocentric bivalent chromosomes through their NOR regions [8].

During spermatogenesis, both the X and Y chromosomes undergo transient inactivation through epigenetic mechanisms such as histone modifications [10, 11]. The interaction of the translocation chromosome with the X chromosome in the sex vesicle interferes with X chromosome inactivation [8]. This interaction has been reported in a male with a balanced translocation [8]. Interference of X inactivation interacts with the gametogenesis in male patients by disturbing the orderly functions of biochemical machinery and results in oligozoospermia or azoospermia.

Luciani *et al*. [8] reported the interaction rate of the translocation chromosome with the sex vesicle as 61% in their study. The rest of the meioses do not involve the interaction of the translocation chromosome with the sex vesicle. This probably explains why not all der(13q;14q) carriers are azoospermic. In our patient, the reason for azoospermia is probably the high percentage of this interaction.

To our knowledge, this is the first report of azoospermia secondary to chromosomal defect of der(13q; 14q) complicated by a pituitary problem. We conclude that relevant physicians have to take into account other causes of azoospermia when evaluating hormone treatment failure in azoospermia as a result of hypogonadotropic hypogonadism.

We informed the patient and offered preimplantation genetic diagnosis (PGD), because we believe that sperm fluorescence *in situ* hybridization analysis will be unbeneficial. During the genetic counseling the patient wanted to try at least one cycle of in vitro fertilization (IVF) and is taking medication 150 IU follitropin alpha every other day and 250 mg choriogonadotropin alpha every other day. If IVF succeeds, PGD will be performed on blastomere biopsies.

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