A Case with Double Translocation and Sjögren's Syndrome

Sjögren Sendromu Tanılı ve Çift Translokasyon Taşıyıcısı Bir Olgu

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ABSTRACT We report an infertile patient with Sjögren's syndrome whose chromosome analysis revealed 45,XX,t(4;8)(q31.3~q32.1;q21.3),der(13;14)(q10;q10). Sjögren's syndrome is a systemic autoimmune disorder characterized by xerostomia and xerophtalmia. Although candidate genes for this condition have been suggested, no certain genetic origin has been reported. This case is unusual for carrying both reciprocal and Robertsonian translocation, having no phenotypical abnormalities other than femoral neck hypoplasia and being diagnosed with Sjögren's syndrome. We suggest that infertility might be due to abnormal segregation pattern during gametogenesis, caused by carrying double translocation. We discussed whether the cause of the Sjögren's syndrome was the disruption of a gene in one of the breakpoints 4q31.3~q32.1 or 8q21.3.

Key Words: Translocation, genetic; Sjögren's syndrome; chromosome aberrations; infertility

ÖZET Bu çalışmada kromozom analizi 45,XX,t(4;8)(q31.3~q32.1;q21.3),der(13;14)(q10;q10) saptanan, Sjögren sendromu tanısı konmuş, infertil bir vaka sunulmuştur. Sjögren Sendromu ağız ve göz kuruluğu ile belirti veren otoimmün sistemik bir hastalıktır. Aday genler tanımlanmış olmakla birlikte, genetik sebebi kesin olarak belirlenememiştir. Sunulan bu olgu biri resiprokal, diğeri Robertsonian translokasyon olmak üzere iki tür translokasyon taşıması, femur boynu hipoplazisi dışında saptanabilen herhangi bir anomali bulunmaması ve klinik olarak Sjögren sendromu tanısı almasından dolayı orjinaldir. Vakada bulunan infertilitenin, resiprokal ve Robertsonian translokasyon taşıyıcılığının gamet oluşumu esnasında anormal segregasyon paterni oluşturmasına bağlı olabileceğini düşünülmüştür. Ayrıca 4q31.3~q32.1 ya da 8q21.3 kromozom kırık bölgelerinde bulunan genlerin Sjögren Sendromu'ndan sorumlu olabileceği tartışılmıştır.

Anahtar Kelimeler: Translokasyon, genetik; Sjögren sendromu; kromozom aberasyonları; kısırlık

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Sjögren's syndrome (SS), clinically characterized by xerostomia and xerophthalmia and general arthralgia is an autoimmune disease with an incidence of 6.9 per 100 000. Environmental factors especially viral infections were suggested to activate the epithelial cells and induce the inflammatory response in patients who are genetically predisposed.[1,2]

Although the immunological pathogenesis of SS is clearly identified, the genetic basis of the syndrome is not yet clear. STAT4 and IRF5 genes that play a role in the Interleukin-1 pathway are thought to be responsible for SS and numerous candidate genes have been suggested so far, located mainly on chromosomes X, 1, 6, 7 and 12.[2,3]

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Translocations, which are common structural chromosomal abnormalities in humans, may be either reciprocal or Robertsonian. Reciprocal translocations are found in about 1 in 500 newborns whereas Robertsonian translocations occur with a prevalence of 1 in 1000.[4]

In general, carriers of the abovementioned translocations do not show any abnormal clinical phenotype, if breakpoints do not damage an important gene or there is no loss of genetic material. Balanced carriers of these rearrangements, although phenotypically normal, may present with infertility, recurrent miscarriage or offspring with an abnormal phenotype after segregation of the translocation at meiosis.[5]

In this case report, we presented an infertile woman who had both reciprocal and Robertsonian translocations, diagnosed with SS and hypoplasia of the femoral neck.

CASE REPORT

A 65 years old female was referred from the Rheumatology clinic with joint subluxations and hypoplasia of bilateral femoral necks. Her parents were consanguineous, but she did not know the degree and information could not be obtained since they had deceased. She has been married for 40 years and did not have any succesful pregnancy. The cause of the infertility has not been studied.

She has been complaining of pain on walking for several years and she had undergone lumber disc hernia operation 6 years ago. Her pain on walking decreased with therapy but she has not been able to stand on her feet for 2 months. The X-ray imaging showed bilateral absence of the femoral necks. Magnetic resonance imaging (MRI) revealed severe deformation of the heads and necks of both femurs.

She also complained from xerostomia and xerophthalmia. She has been suffering from arthralgia of the shoulders, elbows and knees for many years.

On physical examination, her weight, height and head circumference percentages were normal. Hyperextension of both elbows and knees and contracture of the proximal interphalangeal joint of the fifth finger on her right hand were the most significant findings of the physical examination.

The abdominal ultrasonography revealed a smaller right kidney than the left. T-score of the bone mineral density test was -3. Parathyroid hormone levels were increased, calcium and phosphorus levels were normal but urinary calcium excretion (tested in 24-hours urine) was decreased. The erythrocyte sedimentation rate was 40 mm/hour. Additional immunologic tests run for general arthralgia, including antinuclear antibodies, anti-SS-A and anti-SS-B, antimitochondrial antibodies and antineutrophile cytoplasm antibody were negative except for anti-SS-A. She was diagnosed with SS based on salivary gland biopsy, which revealed lymphocytic infiltration.

Cytogenetic analysis was performed from peripheral blood lymphocytes according to standard procedures. High resolution multicolor-banding (MCB) based on microdissection derived region-specific libraries for chromosomes 4 and 8 was carried out as described previously; the method and MCB probe sets were specified in Liehr et al. and the probes in Weise et al.[6,7] Twenty metaphase spreads were analyzed using a fluorescence microscope (Axioplan MOT, Zeiss) equipped with appropriate filter sets to discriminate between a maximum of five fluorochromes and the counterstain diaminophenylindol (DAPI). Image capturing and processing were carried out using an imaging system (MetaSystems, Altlussheim, Germany) for the evaluation of MCB.

Peripheral blood chromosome analysis of the patient revealed a karyotype 45,XX,t(4;8)(q31;q13), der(13;14)(q10;q10). High resolution multicolor-banding (MCB) (6,7) refined the karyotype to 45,XX,t(4;8)(q31.3~q32.1;q21.3),der(13;14)(q10;q1) (Figures 1, 2).

DISCUSSION

We reported an infertile woman with reciprocal and Robertsonian translocation who had a cinical diagnosis of SS.

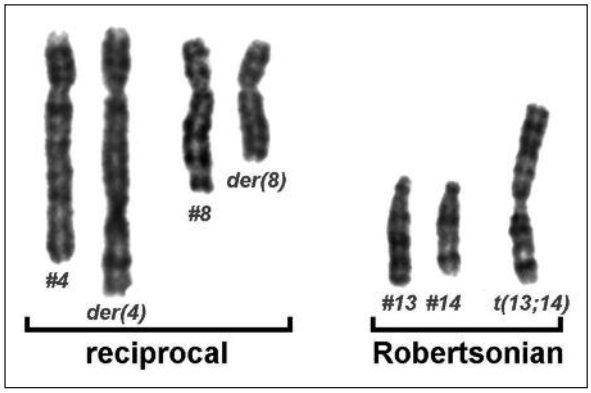

FIGURE 1: Partial karyotype of the present patient showing the reciprocal translocation t(4;8)(q31.3~q32.1;q21.3) and the Robertsonian one: der(13;14)(q10;q10).

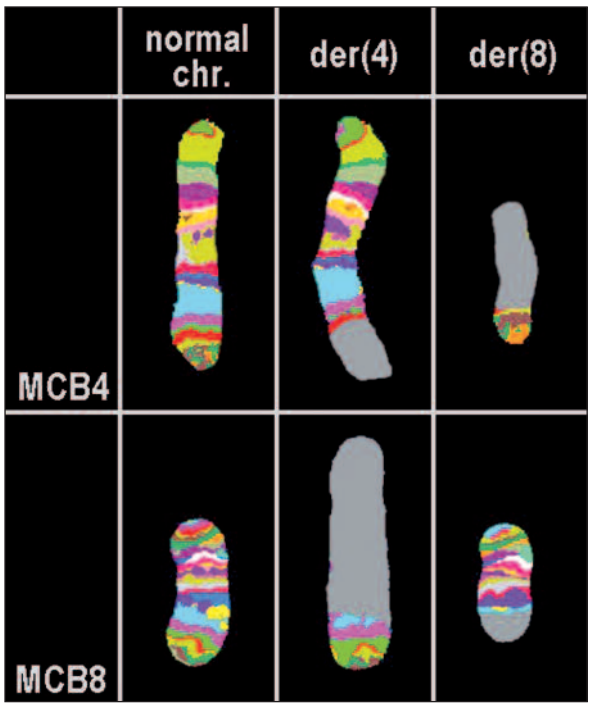

FIGURE 2: Fluorescent in-situ hybridization result after application of the multicolor-banding probe sets for chromosome 4 and 8, defining the breakpoints of the reciprocal translocation as 4q31.3~q32.1 and 8q21.3.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

SS is an autoimmune disease characterized with keratoconjunctivitis sicca, xerostomia, generalized arthralgia and extraglandular features. These findings are due to the lymphocytic infiltration of salivary and lacrimal glands and the other extraglandular organs like lungs, kidneys, stomach, skin, muscle and lymph nodes. As a result of the lenfositic infiltration there could be lesions on target organs in the range of pseudolymphoma and non-Hodgkin lymphoma.[1,2,8] There is no report on the relationship between SS and chromosome 4q or 8q. Further genetic studies may reveal the functions of genes on chromosome 4q31 and 8q23 regions, which could possibly be responsible for SS.

In our patient, renal ultrasonography showed size difference between the kidneys, which may be due to the renal involvement of SS; this must be considered before starting any immunosuppressive therapy in patients with SS.[9]

Pseudohypoparathyroidism has also been previously described in patients with SS; this may explain the increased urinary calcium excretion and elevated parathyroid hormone levels in our patient.[10]

Balanced reciprocal and Robertsonian translocations are the most common structural chromosomal abnormalities in human.[11] However, they are very infrequently together in the same patient and they result in a complicated pattern of forming gametes.

Reciprocal translocation carriers are more likely to have abnormalities in the meiotic process, including fertility failures as a high risk of miscarriage or chromosomally unbalanced offspring; in addition, a high proportion of those cases have secondary infertility.[12-14] Anomalies in any of the acrocentric chromosomes may increase the risk of sterility too. In our patient, infertility could be due to an abnormal pattern of meiotic recombination in abnormal oocytes that showed chromosome-pairing errors. As our patient is both Robertsonian and reciprocal translocation carrier, there is a ratio of 1:9 for segregating of balanced gametes.

Genetic counseling is important to determine the risk of producing unbalanced gametes in the offspring. Although our patient was not at a reproductive age, in principle, assisted reproductive techniques with preimplantation genetic diagnosis may be an option to improve the birth rate in translocation carriers.[15]

Hypoplasia of the femoral necks is thought to be a coincidental finding in our patient; on the other hand, further studies can be performed if patients with similar findings are reported in the future.

In conclusion, this case is unique having both reciprocal and Robertsonian translocations together with SS. Even though the relationship between SS, hypoplasia of the femoral neck, and chromosomal rearrangements is still not clear, our case may be a reference for further studies. This case also reminds us of the often-indicative function of cytogenetic analysis to find potential new candidate gene regions.

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