Recurrent Miscarriages in a Patient with Familial T(1;3), Inv(9) and Thrombophilia

Tekrarlayan Düşükleri Olan Bir Olguda Ailesel T(1;3), Inv(9) ve Trombofili

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ABSTRACT We report that a 23 year-old-woman with recurrent miscarriages associated with t(1;3)(p35;p21.3),inv(9)(p11q11) and heterozygote C677T mutation for Methylen-Tetrahydrofolat-Reductase (MTHFR) gene. Cytogenetic analysis was performed by GTG (Giemsa Trypsin Banding) and C banding methods. Molecular analysis was performed by strip assay. The phenotypically normal patient was found 46,XX,1t(1;3)(p35;p21.3), inv(9)(p11q11) and heterozygote C677T mutation for MTHFR gene. The same balanced translocation was found in patient's mother and brother. In addition the same MTHFR C677T heterozygous mutation was found in patient's mother who had also miscarriages, the karyotype of father was normal. We suggest that an unbalanced translocation during gamete formation, thrombophilic status and inversion 9 might be the cause of recurrent miscarriages in our case.

Key Words: Abortion, habitual; thrombophilia; translocation, genetic

ÖZET Bu yazıda tekrarlayan düşükleri olan t(1;3)(p35;p21.3), inv(9)(p11q11) ve Metilen-Tetrahidrofolat Reduktaz (MTHFR) geni C677T heterozigot mutasyon taşıyıcısı 23 yaşında bir kadın olgu sunuldu. Sitogenetik analizde Giemsa Tripsin Bantlama (GTG) ve C bantlama metodu, moleküler analizde strip test uygulandı. Normal fenotipli olgunun karyotipi 46,XX,t(1;3)(p35;p21.3), inv(9)(p11q11) saptandı. Ayrıca, MTHFR C677T heterozigot mutasyon taşıyıcısı olduğu belirlendi. Olgunun annesi ve erkek kardeşinde de aynı translokasyon bulundu. Ayrıca düşükleri olan annesinde MTHFR geni C677T heterozigot mutasyonu saptandı, babanın karyotipi normaldi. Olgumuzda, dengeli translokasyonlar sonucu oluşan dengesiz gamet, trombofili ve inversiyon 9'un düşüklerin nedeni olabileceği düşünüldü.

Anahtar Kelimeler Habituel abortus; trombofili; translokasyon, genetik

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Balanced chromosome rearrangements are found in 3-6% of couples experiencing recurrent spontaneous abortions.[1] About 50% of all spontaneous abortions are caused by chromosomal abnormalities.[2,3] Carriers of balanced chromosome rearrangements have increased risk of infertility, spontaneous abortion, mental retardation, stillbirth or the birth of a child with multiple congenital abnormalities.[4] A few studies have demonstrated an association between the C677T variant of MTHFR and unexplained recurrent early spontaneous abortion.[5-7] On the other hand, inversion 9 may be one of the causes of recurrent spontan abortion.[8]

CASE REPORT

Informed consent were taken from the patients after the explanation of the procedures. Cytogenetic analysis was performed using phytohemagglutinin-stimulated peripheral blood lymphocyte cultures. Metaphase chromosomes were banded by GTG banding technique and 25 metaphases analysed.[9] Karyotypes were described according to the International System for Cytogenetic Nomenclature (ISCN 1995). We used C banding method for revealing inversion 9.

Molecular analysis was performed by genomic DNA isolated from peripheral blood lymphocytes.[10] We used strip assay kits (Vienna Lab, Austria) for MTHFR C677T, Factor V Leiden G1691A and Prothrombin G20210A gene mutations analysis.

We present a couple with recurrent spontaneous abortions presented to our laboratory for cytogenetic analysis. They were married for 4 years with a history of three consecutive first trimester pregnancy losses. The 23 year-old patient and her 29 year-old husband who were both phenotypically normal and there were no consanguinity between them. Patient's obstetrical work-up including ultrasound and hysterosalpingography were normal. There were no systemic, endocrine, anatomic or environmental risk factors for miscarriage. The woman was pregnant during our study but did not accept amniocentesis to be done.

The patient's karyotype was t(1;3)(p35;p21.3), inv(9)(p11q11) (Figure 1). Balanced reciprocal translocation between chromosomes 1 and 3 and inversion 9 were observed. The break points were: t(1;3) (1qter1p35::3p21.33pter;3qter3p21.3: :1p351pter (Figure 2). C-banding analysis revealed inv(9) (Figure 3). The husband's karyotype was 46,XY normal and semen analysis showed a normal spectrum count.

Thrombophilic factors revealed heterozygous C677T mutation in the MTHFR gene. The factor V Leiden G1691A and prothrombin G20210A mutation were found to be negative. Serum factor 2 protein C and activated protein C resistance levels were 143% (70-120) and 1.25% (4.3-6), respectively.

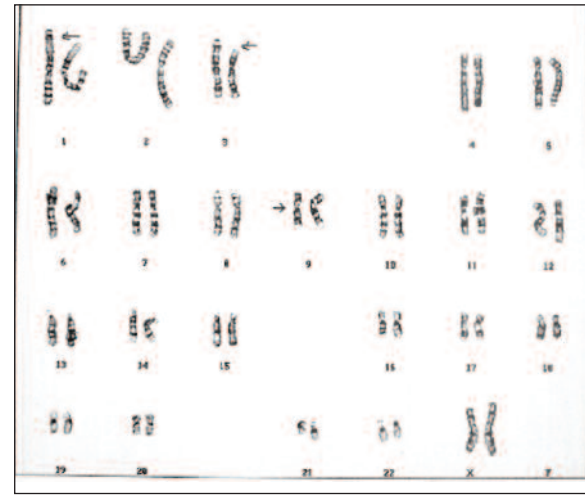

FIGURE 1: G banding karyotype of patient witht(1;3)(p35;p21.3), inv(9) (p11;q11).

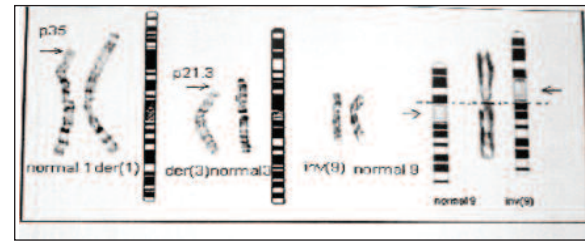

FIGURE 2 Partial karyotipe and schematic drawing of chromosomes 1 and 3 balanced and inv (9) rearrangement.

DISCUSSION

We described a family with reciprocal translocation t(1;3)(p35;p21.3),inv(9)(p11q11) and heterozygote C677T mutation for MTHFR gene may be associated with recurrent pregnancy loss (Figure 4).

Apart from reports in hematological disorders[11] and malignancy, balanced reciprocal translocations have been associated with either spontaneous abortions or a partial monosomic or trisomic infant.[11,12]

The balanced translocations are although associated with congenital malformation to varying degrees, these are known to be compatible with life. Partial trisomy 1q causes severe malformations and these individuals are reported to have a limited life span.[13]

The balanced carrier is healthy but at a high risk of having a chromosomally unbalanced offspring,

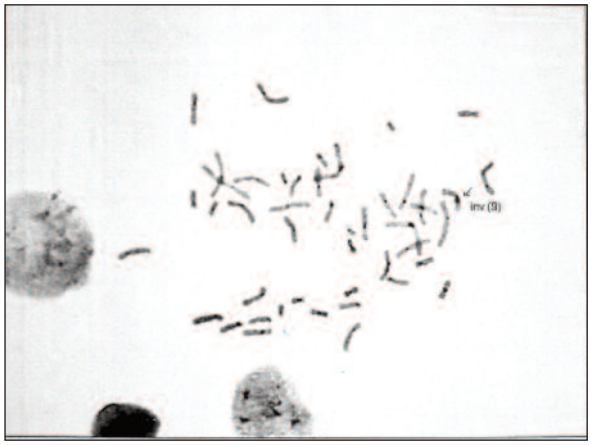

FIGURE 3: C. Banding metaphase image

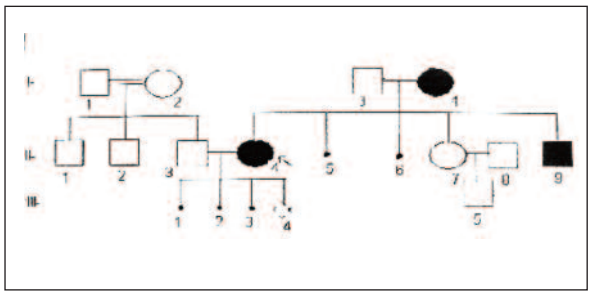

FIGURE 4: Pedigree of the case and her family

leading to a high rate of repeated spontaneous abortions.[14] The increased reproductive failures may result from the selective disadvantage of aneusomic gametes at fertilization or very early spontaneous abortions of unbalanced conceptuses. Adjacent segregation of interchromosomal insertions results in a deletion or duplication.[12] It is interesting to consider the segregation of the quadrivalent at meiosis with reference to the present translocation. Theoretically, the expectation of balanced to unbalanced gametes is 1 : 2 due to the three modes of possible disjunction.[15] Moreover, inversion 9 despite being categorised as a minor chromosomal rearrangement which does not correlate with abnormal phenotypes. Many reports in the literature raised conflicting views regarding the association with subfertility and recurrent abortions.[16] Chromosomal analysis is an important etiological investigation in couples with repeated spontaneous abortions as it helps in genetic counseling and deciding about further reproductive abortions.[17] Preimplantation genetic diagnosis (PGD) can be offered to carriers of balanced translocations. PGD can thus reduce the risk of chromosomally abnormal offspring.[18]

As a conclusion the recurrent abortions might result from the unbalanced distribution of translocation during gamet formation.[19]

In Boue et al.'s study the genetic polymorphisms of MTHFR C677 were found to be associated with unexplained recurrent early spontaneous abortions.[8] MTHFR gene localization is 1p36.3 and translocation breakpoints of our case are t(1;3)(p35;p21.3).

Thus, we suggest that an unbalanced translocation during gamete formation, thrombophilic status and inversion 9 might be the cause of recurrent miscarriages in our case.

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