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Tekrarlayan Fetal Kayıpları Olan Bir Hastada Düşükle İlişkili Mozaik Double Trizomi

Mosaic Double Trisomy Associated with Miscarriage in a Patient with Recurrent Fetal Losses

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ÖZ

Daha önce 5 gebelik kaybı olan 25 yaşındaki gebe kliniğimize başvurdu. Mevcut gebeliği 9. gestasyonel hafta ile uyumluydu ve fetal kardiyak aktivite yoktu, bu nedenle gebelik termine edildi. GTG bantlama tekniği kullanılarak kürtaj materyalinin sitogenetik analizi sonucu 48, XY, + 12, + 15 [5] / 46, XY [25] bulundu. Literatürde bu karyotipe sahip mozaik double trizomi (DT) bildirilmediği görüldü. Trombofili paneli sonucunda heterozigot MTHFR C677T polimorfizmi saptandı. Sonuç olarak, MTHFR polimorfizmlerinin DT gibi nadir kromozomal anormalliklerle ilişkili olabileceği düşünüldü.

Anahtar Kelimeler: Double trizomi, mozaik patern, MTHFR polimorfizm, tekrarlayan gebelik kayıpları, sitogenetik analiz

ABSTRACT

A 25-year-old pregnant woman with a history of five previous miscarriages was admitted to our clinic. Her current pregnancy was also terminated at 9 weeks of gestation due to the lack of fetal cardiac activity. Cytogenetic analysis of abortion material using GTG banding technique revealed 48,XY,+12,+15[5]/46,XY[25] karyotype. Mosaic double trisomy with this karyotype has not been reported in the literature. Thrombophilia evaluation revealed that she had heterozygous MTHFR C677T polymorphism. In conclusion, we may deduce that MTHFR polymorphisms might be related to rare chromosomal abnormalities, such as DT.

Key words: Cytogenetic analysis, double trisomy, mosaicism, MTHFR polymorphism, recurrent pregnancy loss

INTRODUCTION

Chromosomal abnormalities have been observed in approximately 50% of first trimester miscarriages. Single trisomies constitute the vast majority of chromosomal aberrations associated with early pregnancy losses, whilst double trisomy (DT) is a rare entity (1). DT was first reported in 1959 by Ford et al. in a patient with extra copies of chromosome X and chromosome 21 (2). The frequencies of DT ranging from 0.21% to 2.8% have been reported in several studies (3-5). Further, DT may arise in a mosaic state, which was demonstrated in roughly 5% of entire trisomies (6).

Herein, we reported on a pregnancy complicated by DT and also discussed coexisting MTHFR C677T polymorphism as a risk factor. To the best of our knowledge, this is the first case with mosaic DT involving chromosomes 12 and 15.

CASE

A 25-year-old pregnant woman with a history of five previous miscarriages was admitted to our clinic. She had undergone abortion in her first pregnancy at 14 weeks gestation due to anhydramnios. Her second pregnancy had ended in a miscarriage at 19 weeks gestation due to premature rupture of membranes. Both of her first two pregnancies showed normal karyotypes. Her third pregnancy was noted to be an ectopic pregnancy leading to abortion at 5 weeks gestation. Afterwards, she experienced two more miscarriages at 7 weeks of gestation due to the lack of fetal cardiac activity which could not been investigated for chromosomal abnormalities.

Her current pregnancy was also terminated at 9 weeks of gestation due to the lack of fetal cardiac activity. Cytogenetic analysis of abortion material using GTG banding technique revealed 48,XY,+12,+15[5]/46,XY[25] karyotype. (7) Both parents were

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found to have normal karyotypes and physical examinations showed no obvious abnormalities. Thrombophilia evaluation revealed that she had heterozygous MTHFR C677T polymorphism.

DISCUSSION

DT is a rare condition associated with spontaneous miscarriage although, approximately 60% of cytogenetically abnormal spontaneous abortions arise from trisomies, involving mostly single trisomies (5). DT have been documented most commonly in miscarriages related to trisomies involving chromosomes 8, 13, 15, 16, 18, 21, and sex chromosomes (3, 5, 8). Likewise, single trisomies frequently involve those chromosomes (5).

Mosaic trisomies constitute approximately 5% of total trisomies (6). Mosaicism involving the non-acrocentric chromosomes has been more frequently reported compared with the mosaicism involving acrocentric chromosomes (6, 9). Hassold reported the frequency of acrocentric chromosomes in complete trisomies as at least 39%, whereas no mosaic karyotype concerning acrocentric chromosomes was present (6). In our case, we observed a mosaic karyotype involving both acrocentric and non-acrocentric chromosomes. Also we excluded the probability of maternal cell contamination due to lack of metaphases with XX chromosomes in our case (10). Complete DT with aforementioned chromosomal constitution is well-known, however, no mosaic cases have been reported previously (8).

Furthermore, maternal age of the present case is inconsistent with the literature. Despite the strict relationship between advanced maternal age and aneuploidy, no relationship between maternal age and mosaicism has been shown (11). Previous studies regarding the association between DT and maternal age have revealed the mean maternal age as varied between 34.5 and 39.7 (3, 4). Moreover, there are several reports demonstrating the similar relevance between advanced maternal age and DT (5, 8, 12).

DNA methylation is a crucial epigenetic modification of the genome which is involved in regulating many cellular processes such as embryonic development and chromosomal stability (13). MTHFR is an enzyme that participates in the methionine metabolism. Methionine is the precursor of S-adenosyl methionine (SAM) which is the main methyl donor for DNA. MTHFR polymorphisms inhibit the conversion of the dietary folate into an active form, thus inducing an increase of homocysteine and a decrease of the amounts of SAM. Because of the low SAM levels, DNA hypomethylation occurs which may be accompanied by congenital and chromosomal abnormalities (14). In a study of the patients with Turner sydrome, a close association between MTHFR A1298C polymorphism, notably genotype 1298CC, with chromosomal abnormalities has been revealed (15). Additionally, MTHFR A1298C polymorphism was significantly associated with an increased risk of spontaneous abortions due to chromosomal aneuploidy (16). Previous studies also linked MTHFR 677 polymorphisms with spontaneous abortions more than MTHFR 1298 polymorphisms (17). In conclusion, due to the close association of spontaneous abortions with chromosomal abnormalities, we may deduce that MTHFR polymorphisms might be related to rare chromosomal abnormalities, such as DT causing adverse pregnancy outcomes including early pregnancy losses.

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