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Case Report

A Case with Balanced Chromosome Rearrangement Involving Chromosomes 9, 14, and 13 in a Woman with Recurrent Abortion

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A phenotypically normal couple was referred for cytogenetic evaluation due to three consecutive first-trimester spontaneous abortions. Chromosomal analysis from peripheral blood was performed according to standard cytogenetic methods using G-banding technique. The husband's karyotype was normal. The wife's karyotype showed a balanced complex chromosome rearrangement (CCR) involving chromosomes 9,14, and 13. There were three breakpoints: 9p21.2, 14q21, and 13q12.2. The karyotype was designated as 46, XX, t (9;14;13)(p21.2;q21; q12.2). Fluorescence in situ hybridization (FISH) analysis with chromosome-specific libraries of chromosomes 9,14, and 13 was performed to confirm this rare chromosome rearrangement. The result of FISH coincided with that obtained by standard cytogenetic techniques.

Key Words: Balanced complex chromosome rearrangement, fluorescence in situ hybridization

INTRODUCTION

Cytogenetic abnormality is a significant factor in human pregnancy wastage at all stages of gestation. Approximately 1-2% of spontaneous abortions show structural chromosomal rearrangements. Complex chromosome rearrangements (CCRs) have been defined as rearrangements involving two or more chromosomes and at least three breakpoints.[1] It is therefore not surprising that CCR is only rarely seen in constitutional karyotypes. Moreover, some CCRs cannot be interpreted at all with standard cytogenetic methods.

Recently, fluorescence in situ hybridization (FISH), with specific DNA probes for whole chromosomes or for indicated specific chromosomal segments, has significantly improved the characterization of CCRs.[2]

Here we report one case of apparently balanced CCR involving three chromosomes in a woman with recurrent miscarriage.

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CASE REPORT

A Korean couple was referred for chromosome analysis because of a history of three consecutive spontaneous abortions in the first-trimester. The wife was 29 years old, and the husband was 31. They had no liveborn offspring. The gestational and medical histories were unremarkable in both sides. There was no known exposure to recognized teratogens. There was no history of mental retardation, congenital malformations, or recurrent miscarriages in either family. They were healthy and phenotypically normal.

Chromosomal study was done on peripheral lymphocytes from this couple. G-banding was performed on metaphase chromosomes. The result of the wife's karyotype showed that she is a heterozygotic carrier of an apparently balanced CCR involving chromosomes 9, 14, and 13 (Fig. 1). A partial karyotype showed three breakpoints: 9p21.2, 14q21 and 13q12.2 (Fig. 2). The karyotypes of her parent were unknown.

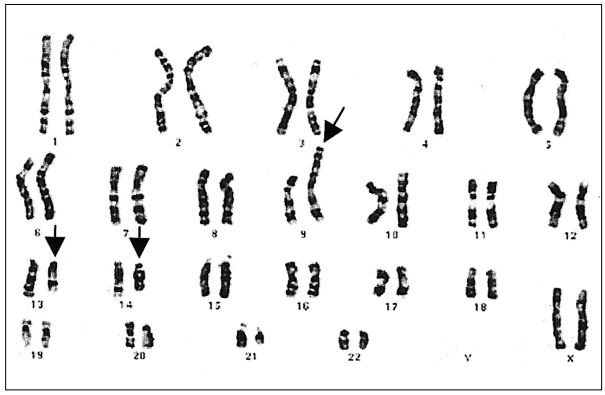

Fig. 1. G-banding karyotype showing a complex chromosome rearrangement between chromosomes 9,14, and 13. Arrows point to the three derivative chromosomes.

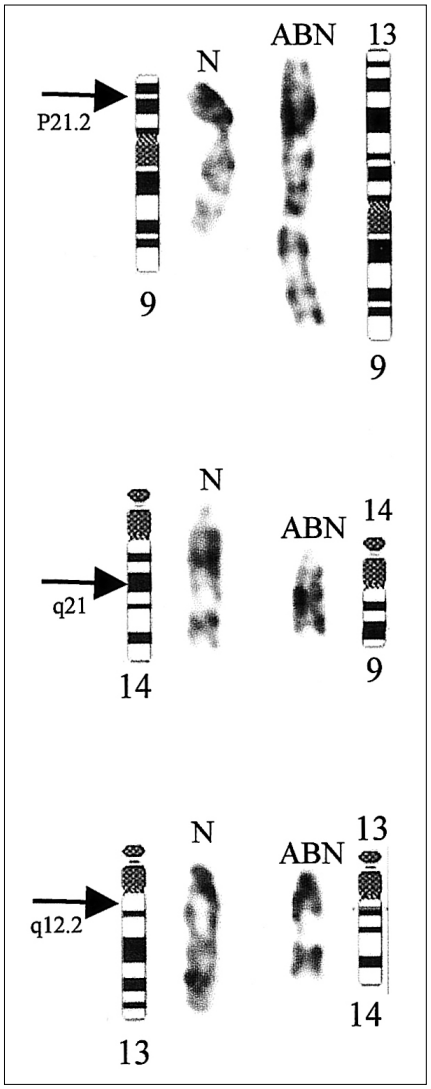

Fig. 2. G-banding partial karyotype of chromosomes 9, 14 and 13 showing balanced complex chromosome rearrangement.

The derivative chromosome 9 contained materials from chromosomes 9 and 13. Chromosome 9 was intact from 9qter to 9p21.2. Distal to this segment was the long arm of chromosome 13 from 13qter to 13q12.2. The derivative chromosome 14 was composed of the satellite, short arm, and proximal long arm of 14. There was a break at 14q21. A distal portion of chromosome 9 from 9pter to 9p21.2 was translocated to 14q21. The derivative chromosome 13 was composed of materials from two chromosomes 13 and 14. Chromosome 13 was intact from 13pter to 13q12.2. Distal to the segment from chromosome 13q12.2 was a segment of chromosome 14 from 14q21 to 14qter.

Fluorescence in situ hybridization (FISH) analysis using whole chromosome painting probes confirmed the involvement of chromosomes 9, 14, and 13 (Fig. 3). Thus, the chromosome constitution was 46,XX, t(9;14;13) (p21.2;q21;q12.2).

The husband's karyotype was apparently normal. This couple was counseled for the prenatal diagnosis in the next pregnancy. Thereafter, they elected to terminate their another fetus because the karyotype according to the second-trimester amniocentesis was determined to be 47,XY, + der(14)t(9;14)(p21.2;q21).

DISCUSSION

Complex chromosome rearrangements (CCRs) are very rare. To date, close to 100 such rearrangements have been reported.[3] They can be familial or de novo and may be balanced or unbalanced. The majority of reported CCRs represent de novo events that appear to have occurred during spermatogenesis. The less frequently reported familial CCRs are transmitted predominantly through females.[4]

Most patients with CCRs represent considerable difficulties in clinical diagnosis. Recurrent pregnancy loss, abnormal phenotype, mental retardation, infertility or subfertility have been reported in otherwise normal carriers of apparently balanced CCRs.[5] So far, there have been three reports concerning repeated miscarriages in otherwise healthy women who underwent chromosomal analysis and resulted to have CCRs.[6-8] However,

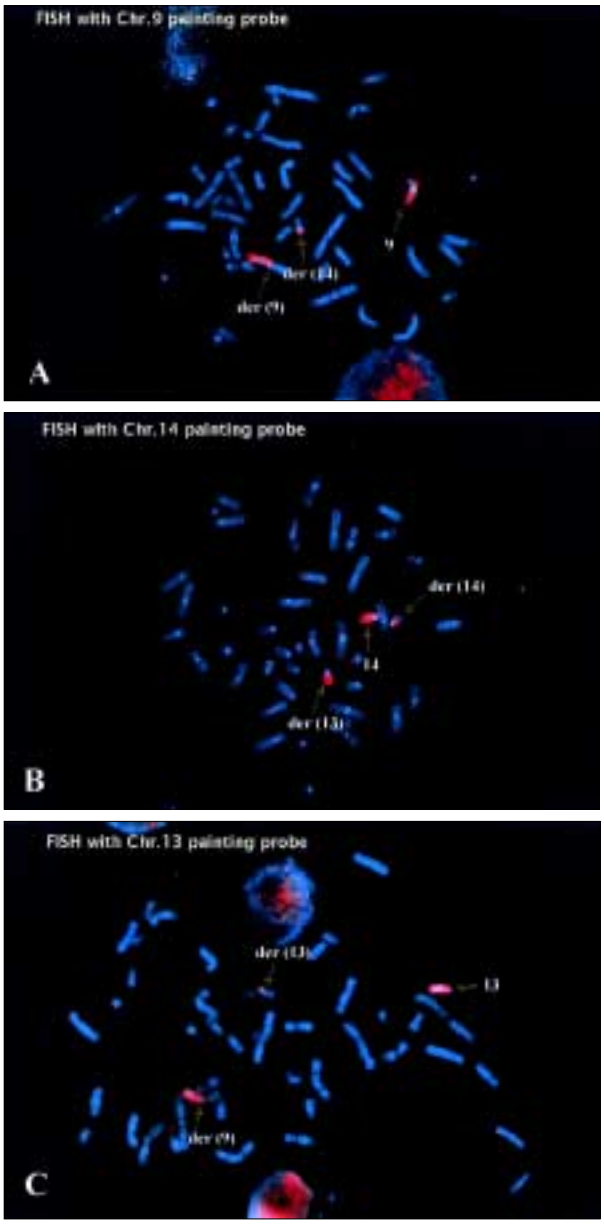

Fig. 3. FISH analysis using whole chromosome painting probes for chromosome 9(A), chromosome 14(B), and chromosome 13(C). Chromosomes were counterstained with diamidino-2-phenylindole.

Phelan et al. reported that most of the CCRs could be detected due to abnormal phenotype.[9]

Review of the literature reveals rearrangements involving 2 to 7 chromosomes with 3 to 10 breakpoints.[10,11] Generally, the more complex the arrangement, the more elaborate the chromosome contortions required to optimize pairing between the rearranged chromosomes and their homologues. Similarly, the more chromosomes involved and the more breakpoints present, the greater the potential number of unbalanced gametes.

The mechanism which initiates the chromosomal breakage is unknown. Exposure to ionizing radiation or immunosuppressive agents before or during pregnancy have been implicated.[12,13] Kousseff et al. suggested that maternal chromosome instability might have led to CCRs.[10] However, no predisposing factors leading to maternal chromosome instability were identified. In the present case, as in most other cases cited in the literature, the patient had no history of receiving radiation or drugs before or during the gestation.

Most of chromosomal abnormalities can be readily diagnosed with standard cytogenetic analysis. However, some CCRs cannot be easily interpreted with routine chromosomal analysis. Recent advances in molecular cytogenetic techniques, such as FISH and spectral karyotyping (SKY), opened a new era of interpretation of deletions, insertions, or visible but subtle translocations.

Phelan et al. have reviewed the outcome of 10 cases of apparently balanced de novo CCRs that were detected prenatally.[9] Four of 10 cases had structural malformations and one had growth retardation and developmental delay. Mercier et al. pointed out that even if ultrasound results are not alarming and even if the cytogenetic analysis, with FISH assistance, do not confirm evidence of chromosomal imbalances, genetic counseling must remain non-committal in the case of prenatally detected de novo CCRs.[3] Unfortunately long term follow-up data on prenatally detected balanced CCRs are lacking until now.

The actual reproductive risks for any CCR carrier will vary depending upon the precise rearrangement involved as well as many other variables. Gorski et al. reported an overall risk of 48.3% of spontaneous abortions and 53.7% of abnormal pregnancy outcome in 25 families with CCRs.[14] Similarly, Batista et al. found in their review of 30 cases, a risk of miscarriage of about 50%, independent of the sex of the carrier parent.[4] The higher risk for miscarriage among balanced CCR carriers suggests that early loss of unbalanced pregnancies may partially explain this observation.

CCR carriers seem to follow the same basic

principles as do simple balanced reciprocal translocation carriers, regarding such aspects as transmission, subfertility in male carriers, segregation, and parental origin.[4] In this case, there was little to offer to improve the future pregnancy outcome. Employing oocyte donation may be an option.

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