Detection of Balanced Homologous Acrocentric Rearrangement rea(14q14q) and Low-grade X-chromosome Mosaicism in a Couple With Repeated Pregnancy Losses

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Chromosome analysis is an important and necessary part of the etiologic investigation in couples experiencing recurrent miscarriage [1]. The mean frequency of chromosome aberrations in couples with recurrent miscarriage is about 5–7% [1–4]. In a study of 2,324 Japanese couples with repeated pregnancy losses, Ozawa et al [4] found chromosome aberrations in 114 couples (4.91%). In their study, approximately 65% of chromosome aberrations detected were reciprocal translocations, 20% were Robertsonian translocations, and 9% were inversions. In a study of 1,400 Tunisian couples with recurrent miscarriage, Elghezal et al [2] found chromosome aberrations in 97 couples (6.93%), with a higher frequency in women than in men (5.21% *vs.* 1.71%). In their study, approximately 33% of chromosome aberrations detected were X-chromosome aneuploidy, 30% were reciprocal translocations, 16% were inversions, and 12% were Robertsonian translocations, but no couples presented with an abnormal karyotype in both parents.

Here, we present a very unusual case of chromosome aberrations in both parents with whom a history of consecutive pregnancy losses was associated. Our case represents one of the most uncommon examples of two chromosome aberrations in a couple with repeated pregnancy losses.

A 29-year-old, gravida 2, para 0, phenotypically normal woman was referred for cytogenetic investigation because of a history of repeated pregnancy losses. The woman had normal internal and external genitalia, regular menstrual cycles, a height of 162 cm, and a body weight of 52 kg. She had experienced one spontaneous abortion and one intrauterine fetal death at 9 weeks of gestation. Chromosome preparations from the blood lymphocyte culture revealed a mos 45,X[4]/47,XXX[1]/46,XX[33] karyotype. Fluorescent *in situ* hybridization analysis using the X-chromosome specific probe (green signal) on 100 interphase lymphocytes of the woman showed one signal in two cells, three signals in two cells, and two signals in 96 cells (Figure A). The result was consistent with low-grade X-chromosome mosaicism for 45,X and 47,XXX. Cytogenetic analysis of the blood lymphocytes from her husband, a 32-year-old phenotypically normal man, revealed a balanced homologous acrocentric rearrangement, rea(14q14q) (Figure B). Polymorphic DNA marker analysis showed that the rea(14q14q) was derived from two different homologous chromosomes 14 (Figure C). The result was a homologous Robertsonian translocation, rob(14q14q). The husband's karyotype was 45,XY,rob(14;14)(q10;q10), and there was no uniparental disomy (UPD) 14.

To date, only a few reports associated with balanced rea(14q14q) have been documented [5–13]. Carriers

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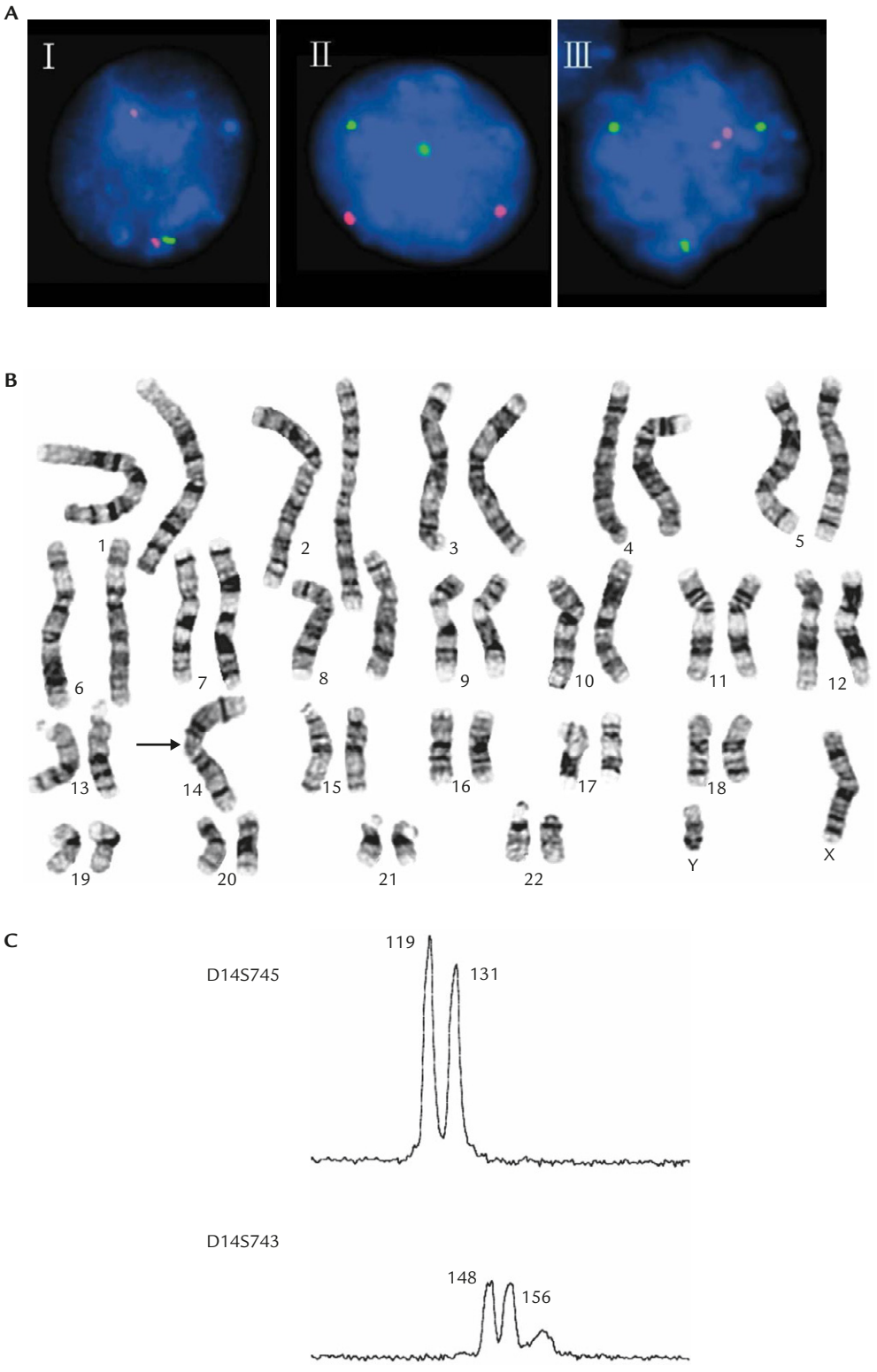

Figure. (A) Fluorescent *in situ* hybridization analysis using bacterial artificial chromosome clones RP11-479E16 (Xp11.21; green signal) and RP11-98B6 (4q11–q12, internal control; red signal) on interphase lymphocytes of the woman shows a cell with one green signal (one X chromosome; left panel), a cell with two green signals (two X chromosomes; middle panel), and a cell with three green signals (three X chromosomes; right panel). (B) A 45,XY,rob(14;14)(q10;q10) karyotype in the husband. The arrow indicates a homologous Robertsonian translocation chromosome, rob(14q14q). (C) Polymorphic DNA marker analysis using chromosome 14q specific markers D14S745 and D14S743 shows a biallelic pattern of the aberrant homologous translocation chromosome, indicating that the aberrant chromosome is a rob(14q14q).

of rea(14q14q), like most carriers of homologous acrocentric rearrangements, are unable to produce normal offspring since all the gametes will be either nullisomic or disomic for the chromosome involved in the rearrangement. The trisomic progenies of the carriers of rea(13q13q) or rea(21q21q) may survive into the second trimester or even to term and such carriers may therefore be ascertained through their abnormal children. However, the trisomy 14 or monosomy 14 progenies of the carriers of rea(14q14q) are incompatible with life, and the carriers of rea(14q14q) have apparently only been ascertained through multiple spontaneous abortions [5–10] or through a UPD14 phenotype (9–13). The chance of a normal karyotype in the fetuses of couples in whom one of the partners is a carrier of balanced rea(14q14q) is theoretically impossible. Genetic counseling in such cases should include the advice that these parents refrain from attempting further pregnancies, and undergo artificial insemination using normal donor sperm (in the case of a male carrier) or normal donor ovum (in the case of a female carrier).

The aberrant chromosome, rea(14q14q), can be an isochromosome 14q, i(14q), or a Robertsonian translocation 14q, rob(14q14q). The i(14q) is derived from a single chromosome 14, and the carrier of a balanced i(14q) may present phenotypic abnormalities of maternal UPD14 or paternal UPD14 depending on the parental origin of the single chromosome 14. Maternal UPD14 is characterized by short stature, muscular hypotonia, precocious puberty, truncal obesity, and variable psychomotor retardation, whereas paternal UPD14 is characterized by severe psychomotor retardation, polyhydramnios, mild contractures of the fingers, and a bell-shaped thorax [14,15]. In our case, the homologous acrocentric rearrangement, rea(14q14q), was derived from two different homologous chromosome 14 and thus was not likely to be associated with UPD14. Since conventional cytogenetic analysis cannot distinguish rob(14q14q) from i(14q), the distinction requires molecular technology using polymorphic DNA markers. Identification of carriers of rea(14q14q) in couples with recurrent miscarriage should include thorough genetic counseling, detailed phenotypic evaluation of the carriers, and molecular investigation of the nature of the rea(14q14q).

Our case had low-grade X-chromosome mosaicism 45,X/46,XX/47,XXX. Low-grade X-chromosome mosaicism has been reported to be associated with recurrent miscarriage. Elghezal et al [2] found that 2.3% (32 of 1,400) of the women with a history of recurrent miscarriage had X-chromosome aneuploidy including 45,X/46,XX (20 cases), 45,X/46,XX/47,XXX (eight cases), 47,XXX (two cases) and 45,X/46,XX/47,XXX/48,XXXX (two cases). Kuo and Guo [16] detected X-chromosome mosaicism in 3.2% (23 of 720) of the women with a history of spontaneous abortions. In their study of 18 patients with spontaneous abortions and X-chromosome mosaicism, e.g. such as 45,X/46,XX/47,XXX (14 cases), 45,X/46,XX (two cases) and 46,XX/47,XXX (two cases), they found that the oocytes of these women were in a suboptimal state of development, resulting in early embryonic demise.

This is the first report detecting balanced homologous acrocentric rearrangement and X-chromosome mosaicism in a couple with repeated pregnancy losses. We emphasize that couples with repeated pregnancy losses should undergo detailed cytogenetic analysis and comprehensive clinical evaluation.

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