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DUAL BALANCED CHROMOSOMAL TRANSLOCATIONS IN A COUPLE WITH RECURRENT PREGNANCY LOSS: CYTOGENETIC FINDINGS AND GENETIC COUNSELING IMPLICATIONS

Pathology

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ABSTRACT

Recurrent pregnancy loss (RPL) is a multifactorial reproductive disorder in which chromosomal abnormalities represent one of the most important identifiable genetic causes[1-3]. Balanced reciprocal translocations are usually phenotypically silent but can lead to reproductive failure through abnormal meiotic segregation[6,7]. We report a diagnostically significant case of a couple with two consecutive first-trimester pregnancy losses over a period of two years. The female partner experienced pregnancy losses at approximately 2.3 months and 3 months of gestation, respectively. Extensive evaluation for non-genetic causes of RPL, including autoimmune, endocrine, hematological, and anatomical assessment, was unremarkable. Conventional GTG-banded karyotyping demonstrated a balanced reciprocal translocation in the female partner, 46,XX,t(4;12)(q31.1;q24.1), and an independent balanced reciprocal translocation in the male partner, 46,XY,t(6;7)(q25;p22), interpreted according to ISCN 2024[8]. Both individuals were phenotypically normal. The coexistence of independent balanced translocations in both partners markedly increases the probability of unbalanced gamete formation and provides a unifying explanation for the recurrent pregnancy losses. This case highlights the importance of couple-based karyotyping and genetic counseling in guiding informed reproductive decision-making[3,9,13].

KEYWORDS

Recurrent pregnancy loss; Balanced translocation; Cytogenetics; Karyotyping; Genetic counseling; Meiotic segregation

INTRODUCTION

Recurrent pregnancy loss (RPL), defined as two or more failed clinical pregnancies, affects approximately 1–2% of couples attempting conception and remains a major clinical challenge[1-3]. The etiology of RPL is heterogeneous and includes uterine structural abnormalities, endocrine dysfunction, autoimmune conditions, inherited thrombophilia, infections, and genetic factors[2,3]. Among genetic causes, chromosomal abnormalities-particularly balanced structural rearrangements-are among the most consistently identified contributors.

Balanced reciprocal translocations are uncommon in the general population but are overrepresented among couples with recurrent pregnancy loss[4,5]. Although carriers are usually clinically normal, rearranged chromosomes may segregate abnormally during meiosis, producing gametes with partial monosomy or trisomy that result in implantation failure or early pregnancy loss[6]. In most cases, only one partner is a carrier, allowing some probability of normal or balanced conceptions through alternate segregation. Independent balanced translocations in both partners are uncommon and introduce additional meiotic complexity, substantially reducing the likelihood of a chromosomally balanced embryo[7]. Conventional GTG-banded karyotyping remains the cornerstone test for identifying such rearrangements in couples with RPL[8].

CASE REPORT

A young couple was referred for cytogenetic evaluation following two consecutive pregnancy losses over a two-year period. The female partner reported spontaneous losses at approximately 2.3 months and 3 months of gestation, respectively. Both losses followed confirmed intrauterine pregnancies, and there was no history of live birth.

The couple's marriage was non-consanguineous. The female partner had no dysmorphic features, chronic medical conditions, or relevant family history, a pedigree chart was not considered informative in this case[9]. Pelvic ultrasonography demonstrated a normal uterine morphology. A structured laboratory evaluation for non-genetic causes of RPL was performed. Autoimmune testing, including lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and anti-β2 glycoprotein I antibodies, was negative. Endocrine assessment, including thyroid-stimulating hormone and prolactin levels, was within reference limits and routine hematological parameters were unremarkable.

The male partner was clinically asymptomatic, with no history suggestive of infertility, congenital anomalies, or systemic illness.

Conventional cytogenetic analysis was performed on peripheral blood lymphocytes at 450–550 band resolution using GTG banding according to standard protocols[15]. Peripheral blood lymphocytes were cultured in RPMI-1640 medium supplemented with 20% fetal calf serum, L-glutamine, antibiotics (penicillin and streptomycin), and phytohemagglutinin. Cultures were incubated for 72 hours at 37°C in a humidified atmosphere with 5% CO_2. Colcemid (10 µg/mL) was added for 45 minutes to achieve metaphase arrest prior to chromosome harvesting. Cells were exposed to hypotonic solution (0.075 mol/L KCl) and fixed with methanol: acetic acid (3:1). Slides were prepared and stained using G-banding. A minimum of 30 metaphases were analyzed for each individual using an Olympus BX-63 microscope (ASI software, version 8.3.2). Karyotypes were assigned according to ISCN 2024 recommendations[8].

Figure Legends

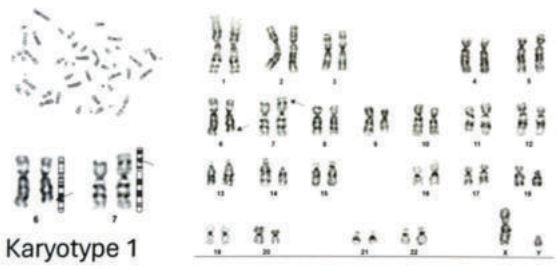

Figure 1. Male partner – GTG-banded karyotype

GTG-banded metaphase karyotype of the male partner revealed a balanced reciprocal chromosomal translocation involving chromosome 6 and chromosome 7, with breakpoints at bands 6q25 and 7p22. The karyotype was designated as 46,XY,t(6;7)(q25;p22) according to ISCN 2024. Analysis was performed on cultured peripheral blood lymphocytes at approximately 450–550 band resolution.

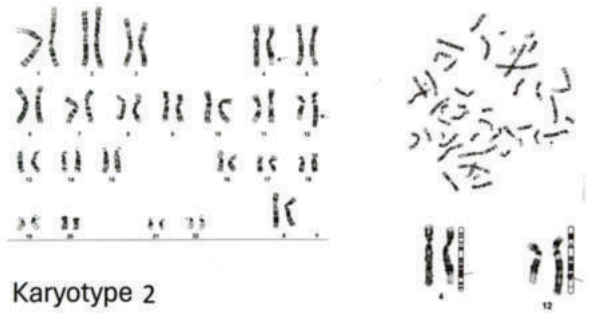

Figure 2. Female partner – GTG-banded karyotype

GTG-banded metaphase karyotype of the female partner revealed a balanced reciprocal chromosomal translocation involving chromosome 4 and chromosome 12, with breakpoints at bands 4q31.1 and 12q24.1. The karyotype was designated as 46,XX,t(4;12)(q31.1;q24.1) according to ISCN 2024. Analysis was performed on cultured peripheral blood lymphocytes at approximately 450–550 band resolution.

No additional numerical or structural chromosomal abnormalities were detected in either individual.

DISCUSSION

Balanced reciprocal translocations are a well-recognized cause of recurrent pregnancy loss due to abnormal chromosomal segregation during meiosis[6,9]. Segregation patterns such as adjacent-1, adjacent-2, and 3:1 generate gametes with partial monosomy or trisomy that are typically incompatible with normal embryonic development[6,7]. The reproductive risk depends on the chromosomes involved, breakpoint locations, and the size of the exchanged segments.

In the present case, pregnancy losses occurred after confirmation of intrauterine gestation, suggesting implantation followed by embryonic demise-a pattern more consistent with chromosomal imbalance than with endocrine or immunological dysfunction[1,2,10]. The absence of alternative non-genetic causes further supports a chromosomal etiology.

Balanced reciprocal chromosomal translocations are uncommon in the general population, with a reported prevalence of approximately 0.2%–0.55% (around 1 in 500 individuals)[9]. Despite this low background frequency, balanced structural chromosomal rearrangements are significantly overrepresented among couples with recurrent pregnancy loss. Multiple studies have shown that 2%–5% of couples with RPL harbor a balanced chromosomal abnormality in at least one partner[3-5].

In contrast, the occurrence of independent balanced reciprocal translocations in both partners, as observed in this case, is exceedingly rare. No large population-based studies specifically address the prevalence of dual translocation carriers within couples. Based on background prevalence data, the theoretical probability of both partners independently carrying balanced translocations is estimated to be well below 1 in 100,000–250,000 couples. Such cases are therefore largely limited to isolated case reports and small case series.

Although rare, dual balanced translocations carry disproportionately high reproductive risk, as chromosomal imbalance may arise independently during both oogenesis and spermatogenesis. This compounded meiotic risk markedly reduces the likelihood of producing a chromosomally balanced embryo and underscores the importance of routine karyotype analysis in both partners during RPL evaluation[3,9].

The translocation breakpoints in this couple involve chromosomal regions 4q31.1, 12q24.1, 6q25, and 7p22, which harbor genes involved in developmental, metabolic, endocrine, and immune pathways, including *FGF2, SH2B3, HNF1A, ESR1,* and *CARD11*. Current evidence does not support consistent dosage sensitivity or a direct causal association between balanced disruption of these regions and recurrent pregnancy loss[11]. The normal phenotype in both partners indicates that meiotic imbalance, rather than direct gene disruption, is the primary mechanism of reproductive failure. Additional molecular testing such as gene sequencing or genome-wide breakpoint mapping is not routinely indicated in phenotypically normal balanced translocation carriers, as such investigations rarely alter clinical management[12].

Reproductive Risk And Genetic Counseling Considerations

Balanced translocation carriers produce multiple categories of gametes due to abnormal chromosomal pairing during meiosis. The rearranged chromosomes form a quadrivalent structure that can segregate in several ways. Alternate segregation produces normal or balanced gametes, whereas adjacent-1, adjacent-2, and 3:1 segregation result in unbalanced gametes commonly leading to implantation failure or early pregnancy loss[6,9]. When both partners carry balanced translocations, abnormal segregation may occur in both the oocyte and the sperm, further reducing the probability of producing a chromosomally balanced embryo[7].

Genetic counseling should explain that pregnancy losses result from chromosomal imbalance in the embryo rather than maternal health, lifestyle, or environmental factors[1,2,10]. Although parental origin of balanced translocations may be explored through karyotype analysis of first-degree relatives, such testing is generally offered only when there is a suggestive family history or when results are expected to influence clinical management, and is not routinely required in all cases of recurrent pregnancy loss[9,10]. Couples should be informed that while natural conception may occasionally result in a viable pregnancy, the risk of further miscarriage and of an unbalanced liveborn child remains elevated[4,6]. Reproductive options should be discussed in a non-directive manner. Natural conception with prenatal diagnosis allows detection of fetal chromosomal imbalance but does not prevent miscarriage[3,10]. In vitro fertilization with preimplantation genetic testing for structural rearrangements (PGT-SR) enables selection of chromosomally normal or balanced embryos before implantation, thereby reducing miscarriage risk[13,14].

The use of donor gametes eliminates the inheritance of genetic risk associated with parental translocations, while adoption offers a non-biological pathway to parenthood that avoids genetic risk entirely. Both options should be included in comprehensive counseling, taking into account personal, cultural and ethical considerations[1,2,10].

CONCLUSION

This case represents a rare but clinically important cause of recurrent pregnancy loss involving independent balanced reciprocal translocations in both partners. Comprehensive cytogenetic evaluation provided a unifying explanation for pregnancy losses and enabled precise genetic counseling. The findings highlight the importance of performing karyotype analysis in both partners during evaluation of recurrent pregnancy loss, as testing only one individual may fail to identify complex chromosomal contributions to reproductive failure.

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