

Case Report

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/apjr.apjr_139_23

Repeated pregnancy losses with multiple aneuploidies and major genomic imbalance: A case report

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Rationale: If one of the partners is having balanced autosomal translocation, it is usually observed that the offspring inherit either normal chromosomes, balanced translocation identical to one of the parent or unbalanced chromosomal rearrangements of the same parental chromosome having translocation.

Concern: A unique case presented with history of 8 miscarriages for genetic counseling. The last abortus material evaluation showed monosomy of chromosome X (Turner syndrome) in all the analyzed cells. There was a history of infertility and also repeated second trimester abortions on the paternal side. On the maternal side, there was a history of intellectual disability.

Diagnose: History of repeated abnormal pregnancy outcomes. Wife's karyotype is normal; however, husband shows translocation between chromosome 4 and 22.

Intervention: Peripheral blood sample around 3 mL was collected for karyotype. Embryo biopsy was done and DNA was extracted and processed for whole exome sequencing.

Outcomes: Wife's karyotype is normal and husband has translocation between chromosome 4 and 22. Surprisingly, the entire pregnancy outcome including embryo screening has different, complete or partial aneuploidies of chromosomes other than chromosome 4 and 22.

Main lesson: Though the translocation in one of the parent is balanced, we have to think beyond traditional ways for evaluating a couple with repeated pregnancy loss as we cannot predict the errors at cell division. Option of *in vitro* fertilization and preimplantation genetic diagnosis in couples having balanced translocations should be discussed so that early intervention can prevent the agony of pregnancy loss.

KEYWORDS: *In vitro* fertilization; Karyotype; Products of conception; Preimplantation genetic testing; PGT; Recurrent pregnancy loss

1. Introduction

Repeated pregnancy loss (RPL) is defined as three or more pregnancy losses below 20 week of gestation. Of all the reported causes, genetic causes are of more concern. Spontaneous abortions account for around 15%-20% of the total pregnancy losses[1]. The incidence of genetic abnormalities is reported to be approximately 50% of all first trimester pregnancy losses, 5% in late trimester and still birth, 7.5% of all conceptions, 10% of spermatozoa, 50% of drug stimulated ova. Almost in 50%-60% of the first trimester pregnancy losses, the cause is genetic and in 70%-80% of the genetic causes it is the chromosomal aneuploidy in the form of monosomy X, trisomy of chromosome 13/18/21 followed by trisomy of chromosome 16/22[2–4]. In RPL, one of the major causes could be balanced translocation in one of the partners. In such cases, the balanced translocation transmits in unbalanced form to the offspring and this leads to either pregnancy wastage or fetal abnormalities based on the extent, break point and type of chromosome involved[5]. The unbalanced forms are usually partially monosomy or partial trisomies of respective chromosomes involved in the parent. Usually, these are inherited from one generation to other[6]. Here, we report a case in which the husband was having balanced translocation between one of the chromosomes 4 and one of the chromosomes 22.

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How to cite this article: Pande S, Babu S, Gawde H, Minde N. Repeated pregnancy losses with multiple aneuploidies and major genomic imbalance: A case report. *Asian Pac J Reprod* 2024; 13(3): 143-146.

Article history: Received: 30 November 2023; Revision: 22 January 2024; Accepted: 27 February 2024; Available online: 31 May 2024

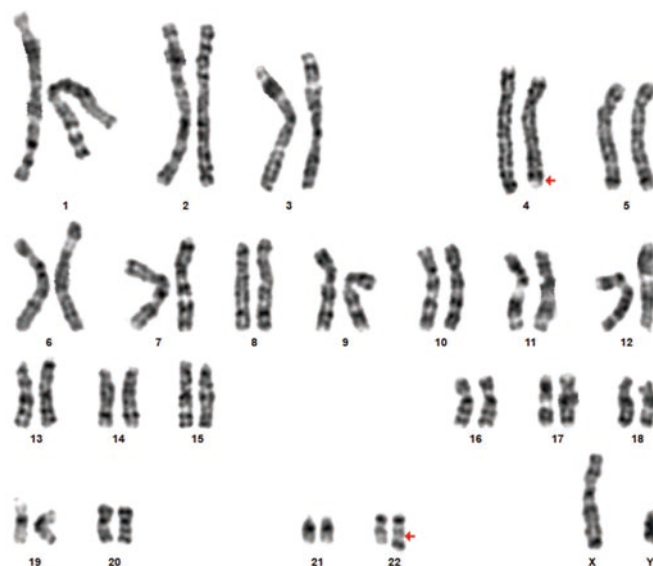


Figure 1. A 36-year-old male partner whose karyotype shows $t(4;22)(q33;q13)$ has a history of repeated abnormal pregnancy outcomes other than involvement of chromosome 4 and 22. His wife's karyotype is apparently normal.

2. Case report

A young couple with history of eight first trimester pregnancy losses was referred to Genetic Research Centre (GRC) for genetic counseling. All the eight conceptions were natural and initial seven were not evaluated. The fluorescence in-situ hybridization (FISH) test done on last products of conception (POC) sample was suggestive of monosomy of chromosome X (or Turner syndrome) in all the analyzed cells. The couple was counseled accordingly and parental karyotype was suggested. Karyotype was done by collecting 3 mL of peripheral blood and planting the culture for 72 h as per the standard protocol. The reporting was done as per the ISCN 2020 guidelines.

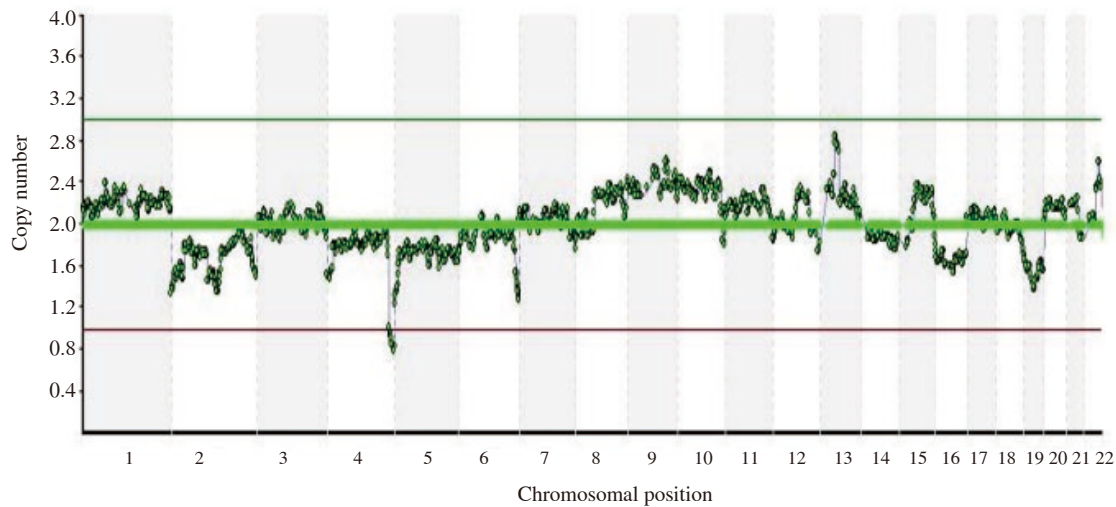
The couple's karyotype revealed normal 46, XX pattern in wife and husband's karyotype was showing 46,XY,t(4;22)(q33;q13). A balanced translocation between one of the chromosomes 4 and one of the chromosomes 22 is at band position q33 and q13, respectively (Figure 1). There was history of infertility and repeated second trimester abortions in the husband's family and a history of infertility and mental subnormality in the wife's family. Posttest counseling was done accordingly to the couple. Various options including prenatal diagnosis (PND) and preimplantation genetic testing (PGT) were discussed. Since patient had already experienced eight miscarriages, they were willing to go for *in vitro* fertilization (IVF). A total of five embryos at day 5 stage were screened by next generation sequencing for chromosomal aneuploidies. Four embryos showed segmental mosaic gain and segmental mosaic loss in multiple chromosomes (Figure 2A, 2B). One of the embryos was having normal diploid status for chromosome 4 and 22; however, surprisingly had segmental mosaic gain and segmental mosaic loss in multiple chromosomes (Figure 2B). Extensive genetic counseling to family members was also suggested.

The study was approved by the Institutional Ethics Committee of ICMR-NIRRH, Mumbai (D/ICEC/Sci-39/41/2023). Informed consent was obtained from all subjects involved in the study. A total of five embryos were screened by next generation sequencing.

3. Discussion

POC is the ideal tissue in RPL for genetic evaluation as it can identify the cause of abortion if any. Appropriate genetic counseling can be offered once the genetic cause and type of genetic abnormality is determined. Additionally, at times couples karyotype may show normal pattern and by evaluating the POC, possibility of gonadal mosaicism can be ruled out. We report a case of eight consecutive first trimester pregnancy losses. The last POC evaluated was suggestive of absence of one of the sex chromosome thereby confirming the cause of pregnancy as chromosomal aneuploidy. To rule out other genetic causes, parental karyotype was done and we found that husband is having a balanced translocation between chromosome 4 and 22. Presence of balanced translocation in one of the parent is reported to be associated with RPL[5]. In light of balanced translocation being cause of RPL, the couple was counseled accordingly and option of PND and PGT was discussed. However, in view of eight miscarriages the couple opted to go for IVF and PGT. At day 5 around 4-5 cells were obtained by embryo biopsy. The biopsy material was subjected to a process called whole genome sequencing. All the tested embryos showed segmental mosaic gain and segmental mosaic loss in multiple chromosomes. One of the embryos was having normal diploid status for chromosome 4 and 22; however, surprisingly had segmental mosaic gain and segmental mosaic loss in multiple chromosomes. As per the Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) Act, 1994,

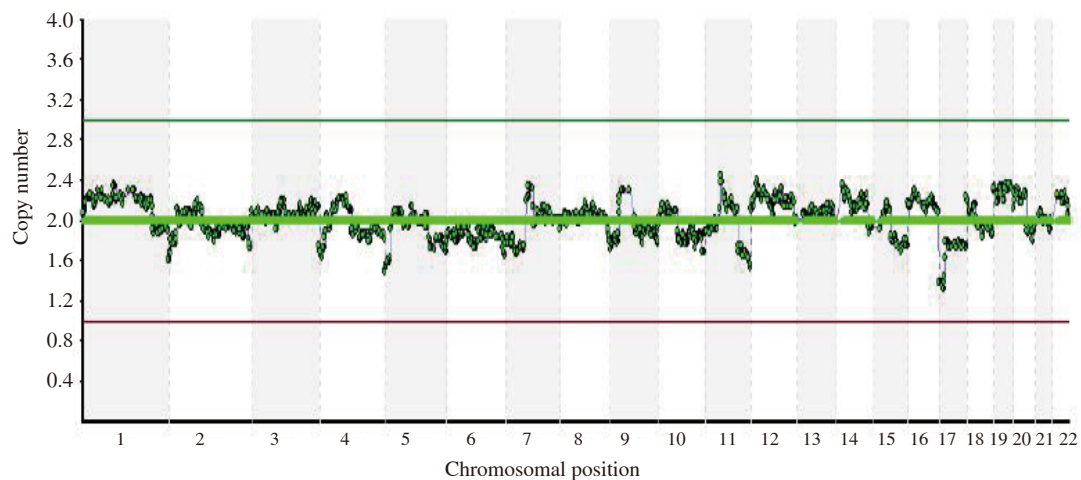
A



Chromosome	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Imbalances	SMG	SML	N	SML	SML	N	N	SMG	SMG	SMG	N	SMG	SMG	N	SMG	SML	N	N	SML	N	N	N

I - Inconclusive, G - Gain, L - Loss, M - Mosaic, N - Normal, SL - Segmental Loss, SG- Segmental Gain, SMG- Segmental Mosaic Gain, SML- Segmental Mosaic Loss

B



Chromosome	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Imbalances	SMG	N	N	N	N	N	SML	N	N	N	SML	SMG	N	N	N	N	SML	N	SMG	N	N	N

I - Inconclusive, G - Gain, L - Loss, M - Mosaic, N - Normal, SL - Segmental Loss, SG- Segmental Gain, SMG- Segmental Mosaic Gain, SML- Segmental Mosaic Loss

Figure 2. (A) A next generation sequencing of the embryo biopsy showing segmental mosaic gain and loss in multiple chromosomes in a couple with history of repeated abnormal pregnancy outcomes. **(B)** A next generation sequencing of embryo showing segmental mosaic gain and loss in multiple chromosomes and chromosome 4 & 22 showing normal pattern in a couple with male partner having balanced translocation between chromosome 4 and 22. Note: As per the PCPNDT Act, 1994, Government of India, sex chromosomes are not shown.

Government of India, sex chromosomes are not shown. Therefore, transfer of embryo was not recommended.

In conclusion, based on the aforementioned results, it can be concluded that there is a possibility of unexpected chromosomal abnormalities in the child when one of the parents have a balanced translocation. Additionally, errors at cell division cannot be

predicted[7]. Some time we have to think beyond traditional ways of evaluating a couple with RPL. While more evidence is required to opine in cases where one or both the partners have a balanced translocation, option of IVF and preimplantation genetic diagnosis in such couples should be discussed to facilitate early intervention and prevent the agony of pregnancy loss.

Conflict of interest statement

There is no conflict of interest.

Acknowledgements

We are thankful to the Director, Dr. Geetanjali Sachdeva ICMR-NIRRH for the guidance. We are thankful to Dr. Shaini Joseph, all the GRC and NIRRH staff for the support.

Funding

The study received financial support from ICMR-National Institute for Research in Reproductive Health (ICMR-NIRRH).

Data availability statement

The related data is made available in the manuscript.

Authors' contributions

Shailesh Pande, Shiny Babu, and Harshavardhan Gawde contributed to development of this manuscript. Shailesh Pande conducted the genetic counseling sessions and Shiny Babu organized the sessions. Shailesh Pande and Harshavardhan Gawde were involved in analysis and Shiny Babu prepared the karyotype reports. Shailesh Pande did the interpretation of all the genetic reports. Shailesh Pande prepared the final draft of the manuscript. Neha Minde involved in documentations for Institutional Ethics Committee (IEC) approval. All authors have read and approved the final version of the manuscript for submission.

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Edited by Lin LY, Lei Y