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Case report

Insight into the 8p23.1 duplication syndrome: Case report of a young women with infertility

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ABSTRACT

Objective: To report the case of a young woman with repeated conception failure, whose karyotype showed an unbalanced complex chromosomal rearrangement involving a large duplication harboring >115 genes and overlapping the 8p23.1 duplication syndrome region. The 8p23.1 duplication syndrome results from a tandem duplication on the short arm of chromosome 8 containing the 4 genes (*GATA4*, *TNKS*, *SOX7*, *XKR6*) responsible for the most common phenotypic features: developmental delay/learning disabilities, congenital heart disease and dysmorphism.
Design: Case report and review of the literature.
Setting: American University of Beirut Medical Center, department of Pathology and Laboratory medicine.
Patient(s): Young woman referred to the genetic clinics for the workup of secondary idiopathic infertility with multiple unsuccessful inseminations and in vitro fertilizations.
Intervention(s): Peripheral blood karyotype analysis from the patient and her parents. Elucidation of the CCR required whole chromosome painting Fluorescent in Situ Hybridization and Chromosomal Microarray.
Main outcome measure(s): The few published reports on 8p23.1 duplication syndrome (<50 cases) describing carriers reveal a wide range of phenotypic consequences with heterogeneous severity. The main outcome is to further understand this syndrome.
Result(s): Chromosomal microarray analysis detected a large (12Mb) pathogenic Copy Number Variant (CNV) at 8p23.3p23.1, overlapping the 8p23.1 duplication syndrome region. This CNV, classified as pathogenic, was shown to carry little significance in our patient.
Conclusion(s): 8p23.1 duplication syndrome display a variable expressivity, ranging from overt syndromic features to minimal effect on the phenotype as shown in this case. Interpretation of prenatal detection of 8p23.1 duplication especially in preimplantation diagnosis is thus challenging. Nevertheless, this case emphasizes the importance of genetic testing in infertile patients displaying a normal phenotype.

1. Introduction

Complex chromosomal rearrangements (CCRs) are defined as structural abnormalities including ≥3 breakpoints on at least 2

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chromosomes [1]. CCRs are rare events, with <255 cases reported involving >3 chromosomes. In phenotypically normal individuals, CCRs are mostly balanced and inherited in families almost always through female carriers. The high complexity of these chromosomal aberrations still constitutes a diagnostic challenge for medical geneticists in terms of their characterization and determination of their clinical effect.

The 8p23.1 duplication syndrome (DS) results from a tandem duplication on the short arm of chromosome 8 containing the 4 genes (*GATA4*, *TNKS*, *SOX7*, *XKR6*) accounting for the most common phenotypic characteristics: developmental delay/learning difficulties, congenital heart disease and dysmorphism [2]. The phenotypic consequences of the duplication, however, are widely variable among carriers. Their severity is guided by the size and location of the duplicated region, and the genes involved. De novo duplications are also more likely to carry phenotypic effects [2]. This rare syndrome is still not yet well characterized, with <50 described patients [3].

We hereby report a familial case of exceptional CCR involving 4 breakpoints, resulting in 8p23.1 DS due to meiotic recombination in an apparently healthy carrier presenting for failure of conception.

1.1. Ethical considerations

Informed consent was obtained from the patient. The review of a single case does not require Institutional Review Board (IRB) review and approval from the Human Research Protection Program at the American University of Beirut.

2. Case report

A young woman was referred for the genetic evaluation of repeated first trimester pregnancy loss following assisted reproductive technology. Patient consent was obtained for the publication of de-identified information. Cytogenetic analysis of the products of conception was not previously performed. The patient had normal puberty, and regular menstrual cycles after treatment for polycystic ovaries syndrome during adolescence. On physical examination, she had a normal height (170 cm) and weight (64kg). No dysmorphic features were detected. Secondary sexual characteristics were well developed and no signs of hyperandrogenism were detected. No behavioral problems or learning difficulties were experienced by the patient. She reported language disability as a child, treated by speech therapy. There was no history of developmental delay, nor documented congenital abnormalities or seizures. Her mother had experienced multiple miscarriages, and her maternal uncle had azoospermia. Her only sister (not available for investigation) has moderate intellectual disability, accompanied by troubles of coordination and orientation. No genetic investigations were previously performed to her family members, to the best of her knowledge. The family history of the husband was non-contributory. He had normal sperm parameters and endocrine evaluation. His physical exam, including a comprehensive urologic evaluation, was normal.

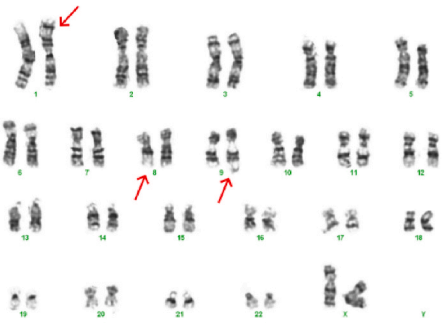

Figure A

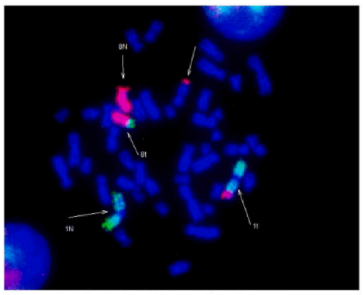

Figure B

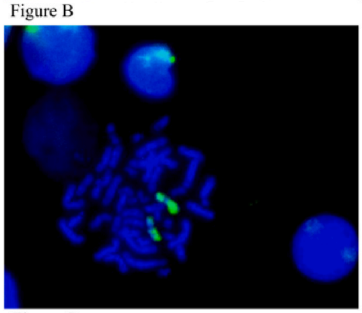

Figure C

Fig. 1. A: G-banded karyotype; Arrows indicate the rearrangements at 1p, 8q and 9q. B: Whole chromosome painting FISH (Green: chromosome 1, Orange: chromosome 8); 1 N: Normal chr 1, 1t: derivative chr 1 containing material from chr 8, 8 N: Normal chr 8, 8t: derivative chr 8 containing material from chr 1, unlabeled arrow: C group chr containing material from chr 8. C: Whole chromosome painting FISH (Green: chr 9); absence of material from chr 9 on other chromosomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.1. Cytogenetics

72-h culture of lymphocytes in Phytohemagglutinin-M (PHA-M) on heparinized peripheral blood for G-banding karyotype was performed. An apparently balanced translocation between the short arm of chromosome 1 and the long arm of chromosome 8, and additional material of unknown chromosomal origin terminally on the q arm of chromosome 9 were detected by metaphase analysis (Fig. 1A). Whole chromosome painting FISH probes (XCP 1 Green, XCP 8 Orange, Metasystems, Germany) ascertained the translocation t(1;8) along with part of chromosome 8 translocating to another unhybridized chromosome, suspected to be chromosome 9 based on karyotype (Fig. 1B). Whole chromosome painting of chromosome 9 (XCP 9 Green, Metasystems, Germany) did not reveal migration of part of chromosome 9 into another partner chromosome, suggesting the absence of involvement of chromosome 9 in a balanced translocation (Fig. 1C).

Chromosomal microarray analysis (CMA) confirmed the presence of an unbalanced translocation in our patient ([GRCh37] 8p23.3p23.1(158,048–11,945,856)×3;[GRCh37]9q34.3(140,751,848–141,020,389)×1).

Parental peripheral blood karyotyping was requested. Maternal karyotyping showed 2 separate balanced translocations: one between the short arm of chromosome 1 at band p31 and the long arm of chromosome 8 at band q21.1, the second involving the same homolog chromosome 8 at its short arm (8p23.1) with the long arm of chromosome 9 (9q34.3) (Fig. 2A). The ISCN nomenclature was designated as follows: 46,XX,t(1;8)(p31;q21.1),t(8;9)(p23.1;q34.3).

The maternal chromosome 8 (rearranged at both ends) was thus modified through meiotic recombination with a normal chromosome 8 at its short arm. Our patient inherited the translocated maternal chromosomes 1, 9 and the meiotically modified chromosome 8 (Fig. 2B).

2.2. Follow up

The DECIPHER database delineates the 8p23.1 DS at the 8:8,242,533–11,907,120 region [4]. It includes 4 patients with a pathogenic duplication (DECIPHER IDs: 326,780, 286,720, 39,162, 384,467), all involving regions covered by the duplication detected in our patient. Because of the association of the 8p23.1 DS with structural heart defects, namely due to the involvement of *GATA4* [OMIM: 600576] in the duplicated region, the patient was referred for cardiac evaluation. No structural abnormalities were detected by cardiac ultrasound.

Genetic counseling was offered to the couple, including options for preimplantation testing with embryo selection and/or prenatal testing.

3. Discussion

We report the first case of a phenotypically normal adult female presenting for repeated abortions, found to have an unbalanced CCR. This chromosomal pattern resulted from the recombination of a different balanced CCR carried by her mother. The prediction of the meiotic behavior of CCR is challenging due to the involvement of multiple patient (age, gender), environmental and chromosomal (number, size, breakpoints) factors in segregation patterns [1]. The mode of meiotic segregation also depends on the structure of the CCR, with possible formation of tetravalent, hexavalent or octavalent configurations facilitating the synapsis of homologous segments. Multiple chromosomal combinations can form following disjunction (symmetrical and non-symmetrical), which can be balanced or unbalanced. Balanced complex translocations more frequently segregate in an adjacent 1 form, leading to unbalanced products [5]. For this reason, the rate of spontaneous abortions is reported to be as high as 50% in carriers of CCRs, with a risk of malformations in live born neonates of 20%. Our patient's rearrangement likely resulted from an alternate 1 segregation, after crossover between the derivative chromosome 8 at its short arm with its normal homolog. The mother carried a balanced complex translocation where the number of breaks is higher than the number of rearranged chromosomes. Most rearrangements in this group have the potential to produce a simpler translocation by recombination during meiosis. Recombinations were found to be non-random [5], and their

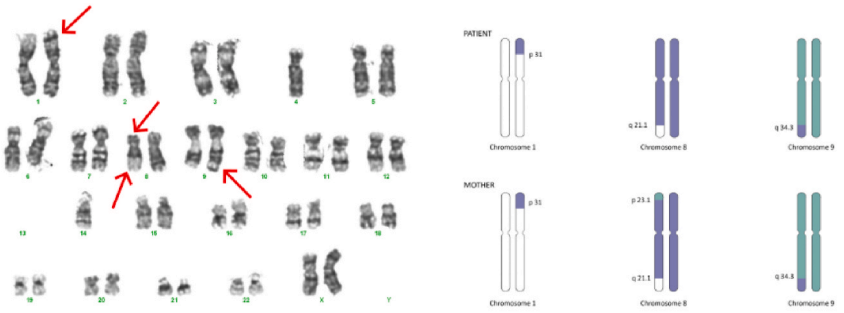

Figure A Figure B

Fig. 2. A: G-banded karyotype; Arrows indicate the rearrangements at 1p, 8p, 8q and 9q. B: Illustration the unbalanced and balanced rearrangements of our patient and her mother.

frequency not proportional to chromosomal length [6]. Instead, the first chromosomes involved in CCRs are unstable and tend to acquire additional breaks/recombination in an attempt to achieve genomic stability, leading to simpler translocations.

The occurrence of CCRs has been postulated to be mediated by serial nonhomologous end joining, microhomology-mediated break-induced replication (MMBIR) and Fork stalling/template switching (FoSTeS) at sites of microhomology and chromothripsis [1]. Several classifications of CCRs have been proposed, categorizing these rearrangements based on the mode of transmission, the number of chromosome breaks, the location and distribution of breakpoints [1]. Based on a structural classification, Kausch's system [7], the most widely used to date, divides CCR into 3 groups. Double 2-way translocations are due to the presence of 2 independent translocations. 3-Way rearrangements are caused by the break of 3 chromosomes and subsequent material exchange. Exceptional CCRS, as in our case, are defined by the occurrence of >1 breakpoint per chromosome. Exceptional CCRs tend to occur de novo and are more likely to harbor phenotypic consequences.

Recurrent pregnancy loss (RPL) is defined as experiencing two or more miscarriages [8]. The American College of Obstetrics and Gynecology (ACOG) recommends offering chromosomal analysis to all couples with RPL along with pathological and cytogenetic analysis of the abortus tissue [8]. The diagnosis of a chromosomal rearrangement allows subsequent prenatal/preconception testing, alleviates the psychological burden of RPL and decreases time loss and costs associated with unsuccessful assisted reproductive procedures. To date, karyotype analysis remains the initial standard diagnostic tool of chromosomal translocations. In the setting of CCRs, karyotyping is limited by the banding resolution and the size of rearrangements [9,10]. This was illustrated in our case, where the ascertainment of the unbalanced nature of the exceptional CCR and the exact breakpoints required the combination of whole chromosome painting FISH and CGH techniques. This integrative approach of combining cytogenetic and genomic testing is essential for the diagnosis of CCRs [11].

Increasing pregnancy outcomes in carriers of reciprocal translocations became possible with the introduction of preimplantation genetic diagnosis (PGD). The success rate is estimated to be around 25% for carriers of translocations involving 2 chromosomes [12]. In CCRs, however, pregnancy outcomes were found to be lower (9%), even after combining results of PGD-FISH and PGD-CGH [13]. The unbalanced nature of our patient's rearrangement involving 4 chromosomes further lowers the chances of a successful pregnancy. The benefits and risks of prenatal/PGD diagnosis should be highlighted during the genetic counseling session.

Counseling in our case is further complicated by the determination of the significance of the potential inheritance of the 8p21.3 duplication by future embryos. In 1998, Barber et al. first presented a series of 7 families with a cytogenetically detected duplication of the p23.1 band at chromosome 8. All carriers had mild or no phenotypic consequences, and it was concluded that the detection of this duplication should be regarded as a variation without underlying clinical significance [14]. However, further reports described children with distinct facial characteristics, developmental delay and congenital anomalies including structural heart defects, syndactyly and preaxial hexadactyly [15–18]. Based on the few described cases, the 8p23.1 duplication interval was delineated between the proximal (REPP) and distal olfactory receptor/defensin repeats (REPD) [19]. It was hypothesized that CNVs of REPP and REPD gene clusters are euchromatic variants carrying no clinical significance while duplications occurring in between should be considered pathogenic [2,16]. Duplications of *XKR6, TNKS*, *SOX7* and *GATA4* were found to be essential for the expression of the clinical consequences associated with the 8p23.1 DS such as behavioral anomalies, developmental delay, and congenital heart diseases, respectively, being expressed in an autosomal dominant manner [3]. A critical interval of 3.68 Mb was identified, encompassing the loci of the 4 responsible genes [18]. However, the clinical manifestations of duplications involving the "pathogenic" interval are not uniform among patients. Variability of penetrance and expressivity manifests in families where an affected child inherits the duplication from an asymptomatic/mildly affected parent. The proband described by Shi et al. received genetic testing only after his sibling underwent prenatal diagnosis for increased nuchal translucency. It was later noted that the proband had a ventricular septal defect and speech delay [20]. The duplication carried by our patient is also highly reflective of the heterogeneity of this syndrome. Despite the indicators of pathogenicity in terms of size (11.79 Mb), inheritance (de novo) and location (overlapping the critical 3.68 Mb region) of our patient's duplication, the clinical expression is restricted to speech delay in childhood. The subtility of clinical manifestations often delays genetic investigations. This variability results in underdiagnosis of the 8p23.1 DS. As such, reporting individual cases is important to further elucidate the significance of this variant.

The interpretation of the pathogenicity of the 8p23.1 duplication remains challenging, especially when detected prenatally [2,3,14–16,18]. Ultrasound findings vary greatly and should be taken into consideration when interpreting the presence of an 8p23.1 duplication in the prenatal period. Observations such as elevated nuchal translucency, cardiac malformations or diaphragmatic hernias constitute indicators of pathogenicity [20].

As previously mentioned, asymptomatic carries of two (or more) translocations usually harbor balanced abnormalities. Our patient, presenting for repeat abortions, was found to carry an exceptional unbalanced rearrangement. In addition, little is known about the 8p23.1 DS, with the majority of reported cases depicting severe phenotypes. This is due to the bias of a population that presents for genetic investigation. The main limitation of our study, however, is the inability to cytogenetically evaluate other family members, especially the sister who seems to have more pronounced features. It would have been interesting to assess this patient for the presence of a DS, further broadening the knowledge on this condition.

4. Conclusion

We reported a young female presenting for infertility found to carry an exceptional, unbalanced, CCR and a large (12 Mb) duplication at 8p23.1. This patient adds to the few reported cases of 8p23.1 DS, often underdiagnosed due to the phenotype heterogeneity. This CNV, classified as pathogenic, was shown to carry little significance in our patient. Reporting of asymptomatic/mildly symptomatic individuals adds substantial information to our understanding of the 8p23.1 DS, including the determination of

pathogenicity when detected in the preimplantation/prenatal setting. Our case also highlights the importance of the integration of multiple classical and molecular cytogenetic techniques to elucidate CCR.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

No data was used for the research described in the article.

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