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Pseudodicentric chromosome originating from an X-autosome translocation in a male patient with cryptozoospermia

Running title: psu dic(22;X) and male infertility

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Established Facts and Novel Insights

Established facts

Infertility is inevitable for male carriers of reciprocal translocations involving X chromosome, regardless of the position of the X chromosome breakpoint.

Novel insights

Pseudodicentric chromosome psu dic(22;X) originating from an X-autosome translocation is a rare event, adding complexity in meiosis progress.

The combination of different cytogenetics approaches can be necessary to give an accurate description of chromosomal rearrangements.

Abstract

Genetic factors are responsible for 15% of male infertility conditions. Numerical and structural chromosomal anomalies are validated genetic factors leading to spermatogenic quantitative defects, with a frequency depending on the severity of the phenotype. Among the structural chromosomal rearrangements, dicentric chromosomes are generally observed in robertsonian translocations or in case of Y chromosome isodicentric. In X-autosome translocations, male carriers are generally infertile, regardless of the position of the breakpoint, due to interrupted spermatogenesis. We report an infertile man bearing an unusual balanced (X;22) translocation, with a centromeric X breakpoint generating a derivative pseudodicentric chromosome (22;X). Extensive cytogenetic analyses were necessary to determine the precise nature of the derivative chromosome. The likely cause of the reproductive phenotype of the patient is discussed based on meiotic chromosomal conformation.

Introduction

Infertility, defined as a failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, is observed in about 10% of couples [Saadati et al., 2020]. Male infertility affects about 7% of the general male population [Krausz et al., 2015; Krausz, and Riera-Escamilla, 2018]. Spermatogenic quantitative defects include 1) azoospermia characterized by the absence of spermatozoa in the ejaculate, observed in 1% of the male population and in 20% of infertile men [Karabulut et al., 2018], 2) cryptozoospermia defined by very low spermatozoa concentration in the ejaculate (≤ 0.1 M/mL) or presence of few sperm in the ejaculate identifiable only after concentration and/or extensive microscopic search [Punab et al., 2017; Zhu et al., 2016], and 3) oligozoospermia corresponding to a low concentration of spermatozoa in the ejaculate (≤ 15 M/mL). Genetic factors are responsible for 20-25% of male infertility [Krausz et al., 2018]. Numerical and structural chromosomal anomalies can cause spermatogenic quantitative defects, with a frequency depending on the severity of the phenotype. In azoospermic men, a frequency of 13-15% chromosomal abnormalities is reported, 93% of which affect the sex chromosomes [Krausz, and Riera-Escamilla, 2018; Mau-Holzmann, 2005]. A lower frequency of chromosomal abnormalities is reported for oligozoospermia (4%), with autosomal chromosomal abnormalities being the most frequent (mainly Robertsonian translocations then reciprocal translocations RCTs) [Krausz, and Riera-Escamilla, 2018; Mau-Holzmann, 2005]. Genetic factors have been identified in approximately 10% of men with cryptozoospermia, with mainly AZFc deletions on Y chromosome [Punab et al., 2017].

RCTs are the most common structural chromosomal rearrangements in humans, producing a quadrivalent configuration during meiosis, with a pattern of chromosome segregation generally unique to each case dependent on the chromosomes involved, the size of the rearrangement, and the nature of the breakpoints [Grzesiuk et al., 2016; Wiland et al., 2014]. Male carriers of RCTs, while phenotypically normal, are likely to experience infertility due to spermatogenic defects, or

reproductive failure linked to quadrivalent mechanics and/or the production of unbalanced gametes. Altered expression of reproductive genes interrupted by breakpoints may also contribute to infertility [Wiland et al., 2014; Harton, and Tempest, 2012]. The question of why some translocation carriers suffer from male infertility and others do not is still unresolved. Nevertheless, male carriers of balanced X-autosome translocations are almost invariably infertile, due to interrupted spermatogenesis [Grzesiuk et al., 2016].

We report a man presenting with cryptozoospermia and bearing an unusual balanced (X;22) translocation, with a chromosome 22 breakpoint mapped at 22q12.1, and a centromeric X breakpoint generating a derivative pseudodacentric chromosome (22;X).

Case report

The proband consulted at 37-year-old for a one-and-a-half-year history of primary infertility. Hormonal assessment was normal (FSH: 13.1UI/l, LH: 6.2 UI/l, inhibin beta: 71 pg/ml, conjugated testosterone: 4.994 ng/ml). A cryptozoospermia was identified in several semen analyses with only very few spermatozoa (< 50 in the whole ejaculate), all of them non-motile, observed in 30 minutes or after centrifugation. Volume, color, viscosity, and pH were otherwise normal. FISH-sperm analysis and TUNEL assay would have been useful to assess the formation of unbalanced spermatozoa and sperm DNA damage, but it was not possible to perform these due to the very low number of spermatozoa. Testis biopsy revealed complete absence of spermatogenesis, fibrous thickening of the basal membranes around all the seminiferous tubules with the presence of rare sclerotic tubules, presence of mature Sertoli cells and non-hyperplastic Leydig cells, and absence of fibrosis or inflammatory infiltrate of the stroma. He had three occasions of urinary tract infection at age 20 years and testis ultrasonographic identified a left type III varicocele and a right epididymal cyst (3.7 mm). His familial history reports a paternal aunt with cancer predisposition but genetic marker was not screened in the proband. The familial history was otherwise unremarkable. His partner was diagnosed with a left fallopian tube obstruction.

Material and methods

Karyotyping

Conventional R-banded karyotype was performed from peripheral blood lymphocyte culture, according to standard protocols with a resolution of 550-band level. Fifty metaphases were analyzed.

Fluorescence in situ hybridization (FISH)

FISH analysis was performed on slides obtained from peripheral blood lymphocyte culture using the following probes: whole chromosome paint (wcp) for X and 22 (MetaSystems, Altlußheim, Germany), D14Z1/D22Z1 centromere probe (Cytocell, Cambridge, UK), DXZ1 centromere probe (Abbott Molecular, Abbott Park, IL, USA), and in-house 22q probes to characterize the 22q breakpoint (available on demand). Metaphase FISH studies were performed according to standard procedures.

Metaphase slides were analysed with an epifluorescent microscope Olympus BX61 and images were captured using Isis® software (MetaSystems, Altlußheim, Germany). Fifteen metaphases were observed for each probe.

Microarray

Oligonucleotide array-CGH was performed on DNA obtained from peripheral blood, using the Agilent Human Genome CGH microarray 180K (Agilent Technologies, Santa Clara, CA, USA) as previously described [Beaumont et al., 2019].

Whole exome sequencing (WES)

DNA underwent WES with SureSelect Human All Exon V7 (Agilent) and sequencing on the NextSeq 500/550 (Illumina). WES data were processed using in-house C-GeVarA pipeline (Constitutional Genetic Variant Analysis). Analysis was performed as previously described (gene-centric and variant-centric approaches) [Tucker et al., 2022].

Results

A 46 chromosomes karyotype was observed, with what appears to be a balanced reciprocal translocation between chromosomes X and 22 in all analysed cells from patient blood (Figure 1a). No increased aneuploidy was noted. FISH was performed to further characterise this abnormality. Involvement of only chromosomes X and 22 was confirmed with the wcp for X and 22 (Figure 1b). Due to the probable involvement of Xq whole arm, X centromeric probe was used and identified one signal on the derivative (X) or der(X) and one on der(22), meaning a breakpoint in the chromosome X centromere. D14Z1/D22Z1 probe was then applied to prove the presence of a dicentric chromosome containing both DXZ1 and D22Z1 sequences (Figure 1c). The shape signal obtained for DXZ1 on the dicentric suggested an inactive state (absence of constriction). Probes targeting chromosome 22 long arm localized the breakpoint at CTA-125H2 (chr22: 26,230,701-26,404,213, 22q12.1, GRCh37) (Figure 1d), disrupting the *MYO18B* gene. Microarray did not identify any pathogenic imbalance, and only variants found with high frequencies in the general population according to the Database of Genomic Variants (<http://dgv.tcag.ca/dgv/app/home>) thus corresponding to polymorphism were noted. WES did not identify any pathogenic variants that could be linked to the patient's phenotype.

The chromosomal abnormality according to International System for human Cytogenomic Nomenclature 2020 (ISCN 2020) [McGowan-Jordan et al.] is: 46,Y,t(X;22)(q10;q12.1).ish der(X)t(X;22)(wcpX+,DXZ1+,wcp22+,CTA-125H2 dim),psu dic(22;X)(q12.1;q10)(D14Z1/D22Z1+,wcp22+,CTA-221G9+,CTA-125H2 dim,DXZ1+,wcpX+).arr(1-22)x2,(X,Y)x1

Discussion

Continuing role of cytogenetics analyses for the evaluation of structural chromosomal abnormalities

We describe an infertile man with cryptozoospermia and a balanced reciprocal non-robertsonian translocation between chromosomes X and 22. Karyotype, FISH, and microarray analyses were

necessary to characterize the chromosomal rearrangement as a pseudodicentric chromosome (22;X) involving a centromeric breakpoint on the chromosome X. We highlight the important role that classical cytogenetics plays in evaluating some types of structural chromosomal abnormalities [Beaumont et al., 2019].

An uncommon balanced RCT with a dicentric derivative chromosome

The centromere is a specialized chromosome locus required for faithful genome inheritance during each round of cell division. Each chromosome generally contains a single region of centromeric DNA, corresponding to a complex chromosomal locus where the kinetochore is formed and microtubules attach during cell division [Stimpson et al., 2012]. Human centromeres are composed of alpha-satellite DNA arranged into higher-order repeat (HOR) units. Pericentromeric DNA is also organized in tandemly and short repeated sequences. These repetitive sequences are generally unstable, promoting DNA breakage leading to structural abnormalities involving centromeric DNA [Barra, and Fachinetti, 2018]. Some chromosomal rearrangements can thus lead to the formation of dicentric chromosomes that harbour two physically linked centromeres.

In humans, dicentric chromosomes can involve any two chromosomes but robertsonian translocations and isochromosome X are more frequent [Stimpson et al., 2012]. Robertsonian translocations, involving acrocentric chromosomes, generate dicentric chromosomes through centric fusion. Isochromosomes, with two centromeres close to each other, can originate from centromere mis-division or U-type exchange. Dicentric chromosomes can also arise from end-to-end recombination after double-strand breakage of two chromosomes, or from chromosomal fusion via telomere deprotection. In male infertility, chromosome Y isodicentric is a known cause that can affect AZF regions, often reported in a mosaic state [Krausz, and Riera-Escamilla, 2018]. In whole-arm translocations, one potential mechanism is non-allelic homologous recombination at centromeric repeats, potentially driven by the high DNA sequence similarity between alpha-satellite repeats [Barra, and Fachinetti, 2018]. Resulting derivative chromosomes are then dicentric with two mixed centromeres. When one breakpoint occurs within the centromere and the other is located juxta-centromeric, only one dicentric derivative chromosome with a hybrid centromere is formed, and the other has a reduced but conserved original centromere [Wiland et al., 2014]. These dicentric chromosomes can exist as functionally dicentric, with the conservation of two active centromeres, particularly in cases of short intercentromeric distance [Barra, and Fachinetti, 2018]. They can also exist as functionally monocentric (pseudodicentric) with inactivation of one of the centromeres, presumed to bring stability for segregation. In such cases, centromere inactivation is likely non-random, with a greater tendency for smaller centromeres to be inactivated. Such inactivation is conferred either by deletion of centromeric DNA sequence or by epigenetic inactivation of one of the two centromeres [Barra, and Fachinetti, 2018].

In our case, a breakpoint occurred on the X centromere leading to the involvement of Xq whole arm, and a reduced centromere on the derivative (X). The other breakpoint was not juxta-centromeric but located on 22q12.1, a region devoid of duplicons and without homology with alpha-satellite DNA, generating a pseudodicentric der(22) with the entire 22 centromere, a reduced X centromere, and a long intercentromeric distance. In line with the centromere inactivation hypothesis, the small-sized X centromere distant from the 22 centromere was inactivated, bringing stability to this non-robertsonian pseudodicentric chromosome (i.e. involving one acrocentric chromosome).

Dicentric chromosomes and male infertility

Chromosome Y isodicentric is one of the most frequent structural rearrangements that cause male infertility [Krausz, and Riera-Escamilla, 2018]. Dicentric chromosomes arising from robertsonian translocations are also usually associated with male infertility, explained by mechanical constraints during meiosis and production of unbalanced gametes [Zhang et al., 2019], and by the tendency of these rearrangements to attach to the sex vesicle (XY bivalent) [Mau-Holzmann, 2005]. Nevertheless, whether robertsonian translocations have an increased infertility rate is somewhat controversial [Barra, and Fachinetti, 2018]. Non-robertsonian pseudodicentric chromosomes have been associated with several developmental syndromes, and with various impact on fertility [Barra, and Fachinetti, 2018]. Rare forms of Y-autosome translocations leading to 45-chromosome karyotypes with a pseudodicentric (Y;acrocentric) has been reported in families with fertile male carriers [Wimmer et al., 2006; Morales et al., 2007] but also in oligoasthenozoospermia [Jia et al., 2019]. Recently a pseudodicentric (9;21) [Beaumont et al., 2019] and a dicentric chromosome with centromeric fusion dic(9;13) have been associated with oligo and azoospermia, respectively [Wiland et al., 2014]. Regarding X-autosome translocations, male carriers are generally infertile with azoospermia or severe oligozoospermia, regardless of the position of the breakpoint, due to interruption of the spermatogenesis [Grzesiuk et al., 2016]. To date, 31 such translocations have been reported in infertile man [Choi et al., 2020; Grzesiuk et al., 2016] with three t(X;22) linked with azoospermia (Table 1). Most deleterious effects on spermatogenesis are observed in RCTs if acrocentric chromosomes are involved [Wiland et al., 2014]. In our patient, it is likely that the pseudodicentric chromosome (X;22) causes infertility due to the involvement of X chromosome, but unfortunately, parental karyotypes were not available to check whether the rearrangement was inherited from a parent. Although paternal carriership is unlikely, in women, X-autosome translocations are associated with primary ovarian insufficiency in 50% of cases [Di-Battista et al., 2020] therefore suggesting the possibility of a maternal transmission, as previously reported [Grzesiuk et al., 2016]. Furthermore, the primary infertility of this couple could also be linked to bilateral fallopian tube obstruction of the woman.

Origin of male infertility in RCT carriers

1) Male infertility can be linked to spermatogenetic arrest. In RCT carriers, azoospermia is often due to an arrest at the first meiotic division of gametogenesis, due to the efficient meiotic cell cycle checkpoints in male gametogenesis. The main factors that affect the fertility of carriers are the position of breakpoints and the presence or absence of chromosomal recombination, both acting to hold together the arms of the quadrivalent in order to avoid asynapsed regions. When such open configurations are created, the quadrivalent will try to survive at the pachytene checkpoint through heterologous synapsis corresponding to a state of complete pairing, or through attachment of asynapsed regions to other ones like in the sex vesicle. This pairing with sex vesicle is responsible for the spreading of its inactivation to genes that may be necessary for the survival of the meiotic process. If no indispensable gene is silenced, the asynapsed regions and their attachment to the sex vesicle will generate an abnormal disposition of the quadrivalent on the meiotic spindle, triggering the meiotic spindle check-point. Both situations lead to cell destruction [Oliver-Bonet et al., 2005]. The aim of the quadrivalent is thus to avoid open configurations with asynapsed regions, to survive during meiosis, and pass the checkpoints. Thus, in our case, defective spermatogenesis could be explained by association of the translocated 22 chromosome to the sex vesicle and spreading of inactivation into the active chromatin of chromosome 22 leading to the silencing genes necessary for meiosis and subsequent cell death and male infertility [Grzesiuk et al., 2016]. Furthermore, chromosome 22 binds to its homologous chromosome by only one or two chiasmata during meiosis and the loss of a single chiasma between chromosomes 22 is likely to cause errors in chromosome pairing and migration during meiosis [Grzesiuk et al., 2016]. Abnormal pairing due to the presence of two X centromeres may also be a factor leading to a defective meiosis. Above all, infertility is inevitable for male carriers of RCTs involving X chromosome, regardless of the position of the X chromosome breakpoint [Oliver-Bonet et al., 2005].

2) Male reproductive defects can also be the consequence of unbalanced existing spermatozoa (Figure 2). In theory, abnormal segregation at meiosis can be supposed, with formation of unbalanced spermatozoa leading to the occurrence of partial trisomy or monosomy X or 22 in the offspring. No evidence of abnormal segregation at meiosis had been noticed in the patient or his family. If sufficient spermatozoa were detected in our patient, FISH-sperm analysis could assess the formation of such unbalanced spermatozoa, raising the potential for preimplantation genetic diagnosis after microsurgical testicular sperm extraction. Other therapeutic options include sperm donation or adoption.

3) Another hypothesis to explain male infertility would be the presence of key genes for male reproductive function at the breakpoint of the chromosomal rearrangement. In our patient, *MYO18B* was interrupted at chromosome 22 breakpoint. *MYO18B* (OMIM*607295) is involved in autosomal recessive Klippel-Feil syndrome 4. The patient did not present with myopathy nor facial dysmorphism,

furthermore, *Myo18b*-null heterozygous mice have been reported healthy and fertile discounting the potential involvement of *MOY18B* in the patient's reproductive phenotype [Ajima et al., 2008]. Thus this gene could not be linked to reproductive defects in human or animal models. The search for variants in such key genes is part of the workup to unravel aetiology in male patients with idiopathic infertility. For 40% of these patients, the cause of infertility remains unknown despite a first-tier genetic screening [Krausz, and Riera-Escamilla, 2018]. Massively parallel sequencing assays represent now the most promising approach for the discovery of genetic aetiology of idiopathic male infertility [Krausz, and Riera-Escamilla, 2018]; however, they do not circumvent the need for cytogenetic analyses, which detect variants that escape detection by most genome sequencing approaches like this case of dicentric chromosome. For example, whole genome sequencing is currently limited in detecting low-level mosaicism, in studying repetitive DNA sequences, gaps, and unmapped sequences [Hochstenbach et al., 2019].

Conclusion

This case strengthens the role of X-autosome RCTs and dicentric chromosomes in male infertility. In X-autosome RCTs, X chromosome partners and breakpoints are numerous making each case a singular anomaly. Morphological approaches were necessary to show the formation of a dicentric chromosome. This underlines the need in some cases to combine different approaches to give an accurate description of the chromosomal rearrangement and accurate genetic counselling.

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Statement of Ethics

Written informed consent was obtained from the patient for genetic analysis and publication of this case report and any accompanying images. All procedures were in accordance with the ethical standards of the Ethics Committee of Rennes University Hospital and the French law.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

There are no linked research data sets for this paper. Data will be made available on request.

Author Contribution

S. Jaillard designed the study. L. Akloul, C. Pimentel, L. Freton, and S. Odent were involved in patient care. S. Toujani, L. Mary, E. Launay, and S. Jaillard acquired, analyzed, and interpreted the data. M.A. Belaud-Rotureau participated in the project supervision. S. Jaillard, S. Toujani, and E.J. Tucker wrote the manuscript. E.J. Tucker critically reviewed the manuscript, which was approved by all authors.

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Legend to figures

Figure 1: Karyotype and FISH results

1a: karyotype with chromosome 22, derivative (22), and derivative (X); 1b: whole chromosome paint showing presence of chromosome X (green) on the der(22) and of chromosome 22 on der(X); 1c:

presence of D14Z1/D22Z1 (red) on chromosome 22 and der(22), presence of DXZ1 (green) on der(22) and der(X); 1d: presence of CTA-221G9 (red) on chromosome 22 and der(22), and of CTA-125H2 (green) on der(22) and der(X) (splitted probe)

Figure 2: Pachytene configuration in prophase I of meiosis

Black: chromosome 22; Dark red: chromosome X; Dark purple: chromosome Y; Grey: 22 centromere; Light red: X centromere; Light purple: Y centromere; Blue: PAR2; Green: PAR1

X-autosomal Translocation	Infertility Diagnosis	Origin of Translocation	Reference
(X;1)(p22.3;q25)	Azoospermia	Unknown	From [Choi et al., 2020]
(X;1)(p-;q+)	Oligospermia	Maternal	
(X;2)(q13;p21)	Azoospermia	Unknown	
(X;2)(p22.3;q32.3)	Prepubertal	Maternal	
(X;2)(q27;p12)	Azoospermia	Maternal	
(X;3)(q26.1;p11.2)	Azoospermia	Maternal	
(X;3)(q26;q13.2)	Azoospermia	Maternal	
(X;4)(q27;q25)	Prepubertal	Maternal	
(X;5)(p22.2;p12)	Azoospermia	Maternal	
(X;5)(q28;q11)	Azoospermia	Unknown	
(X;5)(q28;p13)	Prepubertal	Maternal	
(X;5)(q28;q29)	Azoospermia	Unknown	
(X;8)(p22;q11)	Azoospermia	Unknown	
(X;9)(p22.2;q31)	Azoospermia	Maternal	
(X;11)(q26;q21)	Azoospermia	Unknown	
(X;12)(q22;p12)	Prepubertal	Maternal	
(X;12)(p22;q15)	Azoospermia	Maternal	
(X;14)(p11.4;p12)	Azoospermia	Maternal	
(X;14)(p22;q21)	Prepubertal	Unknown	
(Xp-,14q+)	Azoospermia	Unknown	
(X;15)(p11;p1)	Oligospermia	Unknown	
(X;15)(p11.3;p1)	Oligospermia	Maternal	
(X;17)(q13;q21)	Prepubertal	Maternal	
(X;18)(q11;p11.1)	Oligospermia	Maternal	
(X;19)(q22;q13.3)	Azoospermia	Unknown	
(X;20)(q10;q10)	Oligospermia	Maternal	
(X;21)(q23;q11)	Azoospermia	Unknown	
(X;21)(q27;q11)	Prepubertal	Maternal	
(X;22)(q25;qter)	Azoospermia	Unknown	
(X;22)(q26;q11)	Azoospermia	Unknown	
(X;22)(22qter→22q11.2::Xp22.3→Xqter; 22pter→22q11.2::Xp22.3→Xpter)	Azoospermia	Maternal	[Grzesiuk et al., 2016]
(X;22)(q10;q12.1)	Cryptozoospermia	Unknown	Present case

Table1

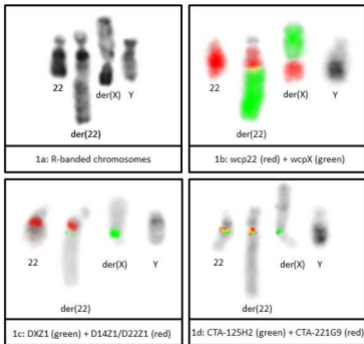


Figure 1

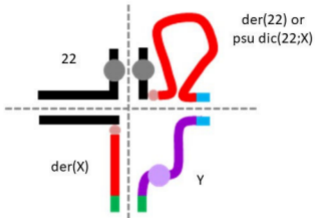


Figure 2