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A constitutional complex chromosome rearrangement involving meiotic arrest in an azoospermic male: Case report

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Complex chromosome rearrangements are rare aberrations that frequently lead to reproductive failure and that may hinder assisted reproduction. A 25-year-old azoospermic male was studied cytogenetically with synaptonemal complex analysis of spermatocytes from a testicular biopsy and fluorescence *in situ* hybridization (FISH) of lymphocytes. The spermatocytes showed a pentavalent plus a univalent chromosome. Cell death occurred mainly at advanced pachytene stages. The sex chromosomes were involved in the multiple, as shown by their typical axial excrescences. Two autosomal pairs, including an acrocentric chromosome (15), were also involved in the multiple. FISH allowed the definite identification of all the involved chromosomes. An inverted chromosome 12 is translocated with most of one long arm of chromosome 15, while the centromeric piece of this chromosome 15 is translocated with Yqh, forming a small marker chromosome t(15;Y). The euchromatic part of the Y chromosome is joined to the remaining piece of chromosome 12, forming a neo-Y chromosome. The patient shows azoospermia and a normal phenotype. The disruption of spermatogenesis is hypothetically due to the extent of asynaptic segments and to sex-body association during pachytene. This CCR occurred '*de novo*' during paternal spermatogenesis. Meiotic analysis and FISH are valuable diagnostic tools in these cases.

Key words: azoospermia/complex chromosome rearrangement/FISH/human meiosis/synaptonemal complex

Introduction

Complex chromosome rearrangements (CCRs) are structural aberrations involving at least three chromosomes and three or more chromosomal breakpoints (Pai *et al.*, 1980). Most of the patients with CCRs are women (Gorski *et al.*, 1986).

Most of the women with CCRs have been identified because they give birth to malformed children or have repeated abortions (Batista *et al.*, 1994), while most of the males with CCRs were found in men showing infertility problems (Siffroi *et al.*, 1997). Usually, these men are sterile because of hypospermatogenesis or spermatogenic arrest. Presumably, this arrest stems from the complexity of the observed meiotic configurations (Chandley, 1981).

CCRs were not described in any of the cytogenetic surveys of newborn infants (Jacobs *et al.*, 1974; Hamerton *et al.*, 1975; Nielsen and Sillesen, 1975). Therefore, the occurrence of CCRs is very low, and only ~100 cases have been recorded (Joyce *et al.*, 1999; Cai *et al.*, 2001; Battisti *et al.*, 2003). In ~70% of the cases, the patients had normal phenotypes and were detected because of reproductive problems.

The CCRs are classified into two groups: familial and *de novo*. These two groups are distinguished by the numbers of breakpoints, ≤ 4 in the former type and >4 in the latter (Kousseff *et al.*, 1987). In most of the familial cases (having between three and four breakpoints), the phenotype is normal in the apparently balanced carriers but they may have a significant risk of reproductive failure (Lespinasse *et al.*, 2003).

Half of the *de novo* CCRs have >4 breakpoints and are associated with multiple malformations, even though they are apparently balanced. Those with four breakpoints may show either abnormal or normal phenotype (Walker *et al.*, 1985; Gorski *et al.*, 1986; Tupler *et al.*, 1992). As the CCRs are not always identified with conventional cytogenetic studies, fluorescence *in situ* hybridization (FISH) (Astbury *et al.*, 2004) and meiotic analysis (Solari and Rey Valzacchi, 1997; Solari, 1999) are useful tools for an accurate diagnosis.

We report here the case of an azoospermic male with a CCR, where three chromosomes are involved (12, 15 and Y) and four breakpoints were observed. The present study shows a deep disturbance of spermatogenesis occurring at the late pachytene stages which leads to the cell death of the vast majority of spermatocytes and the lack of spermiogenesis. The possible mechanisms underlying this disturbance are discussed.

Materials and methods

Case report

The patient is a 25-year-old man consulting for genetic assessment because of primary infertility. He is the first child born from unrelated parents, and has a younger brother, whose fertility status was not studied. The parents had a spontaneous abortion of unknown origin. The mother has no siblings, while the father has three brothers. One of them has normal progeny and the other two died before marriage. Each of the parents came from a large family. The patient had surgery for hydrocele at 8 months of age. The proband is 170 cm tall, weights 85 kg and his sex characteristics are normal. Andrological examination gave normal results. He has completed tertiary education. The analysis of the ejaculate showed azoospermia.

Slide preparation

For chromosome analysis from peripheral blood cultures, slides were made following standard cytogenetic procedures (C-banding and G-banding). Fresh slides prepared in the same way were used for FISH. Microdeletions in the AZF region were tested with multiplex PCR for this segment of the Y chromosome.

FISH

FISH studies were performed according to the protocols provided by the manufacturer (Cambio Ltd, Cambridge, UK), using indirectly labelled, whole-chromosome painting (WCP) probes specific for the X, Y, 15 (Cambio Ltd) and Y centromeric, and a probe for the Prader–Willi–Angelman-specific locus (15q11–13) (Oncor, Gaithersburg, MD). Another WCP probe was used for the entire chromosome 12 and a probe for chromosome 12pter was used to label this region. Both probes for chromosome 12 were obtained by microdissection in a local laboratory. Probe detection was carried out with fluorescein isothiocyanate (FITC; or rhodamine in the case of WCP for chromosome 12) and counterstained with 4′,6-diamidino-2-phenylindole (DAPI) or propidium iodide (PI). A Leica DM microscope fitted with a double-band pass filter and single-band filters was used for observation and registering of FITC and PI or DAPI in 35 mm negative film (400 ASA and 100 ASA, Kodak, Rochester, MN).

Testicular histology and fine structural observations of synaptonemal complexes

Bilateral testicular biopsies were performed as indicated by the andrologist after the approval of the corresponding ethics committee. Biopsies were indicated for routine histology and attempted sperm collection. The recovery of spermatozoa for ICSI treatment was tried with the largest piece of the biopsy (with negative results). One small testicular piece was processed for routine histology, a second one for meiotic studies with light microscopy, and a third piece was used for fine structural studies. Most of this piece was used for microspreading of synaptonemal complexes (SCs) from spermatocytes at pachytene, according to previously described methods (Solari, 1998). Another aliquot was fixed in 2% glutaraldehyde, post-fixed with 1% osmium tetroxide, embedded in Araldite and sectioned in thin (0.08 μm thick) and semi-thin (0.5 μm thick) slices for electron and light microscopy, respectively.

Electron microscopy of spread SCs and sections was made with a Siemens Elmiskop.

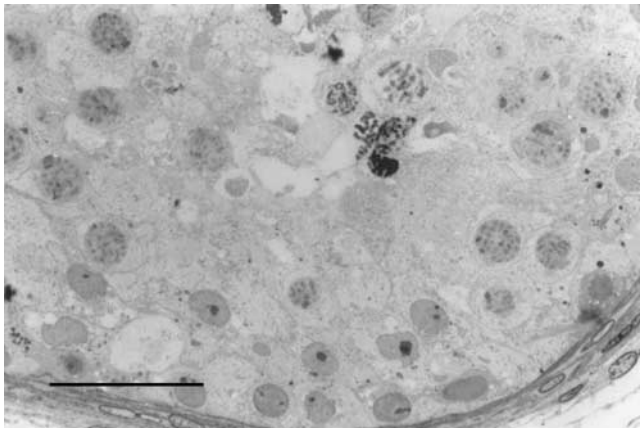

Figure 1. Histology of the testicular biopsy. No sperm or spermatids are seen. Apoptotic spermatocytes are seen at the upper centre. Bar = 50 μm.

Results

Histological findings

The biopsy showed a uniform appearance: there were no seminiferous tubules with full spermatogenesis, and no tubules with 'Sertoli cell-only' features were observed. All the tubules showed spermatogenic arrest at the first spermatocyte level, especially at the late pachytene stage. Large numbers of primary spermatocytes were found in early and mid-pachytene stages. A very low number of metaphase I cells was seen, and all of these cells had an apoptotic appearance. No spermatids or mature sperm were seen in these tubules, in agreement with the observation of the ejaculates (Figure 1).

Cytogenetic investigation

The karyotype shows 46 chromosomes, with one small metacentric marker and two abnormal chromosomes, 12 and 15 (Figure 2). The small marker chromosome has an entire heterochromatic arm, which shows a strong C+ banding and deep DAPI staining (see below). In G-banded metaphases, no

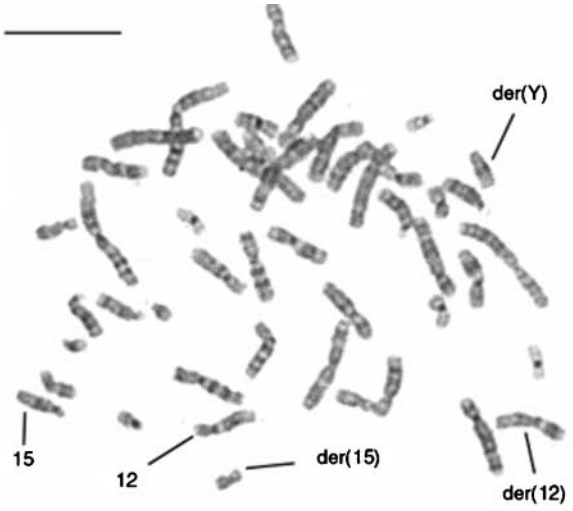

Figure 2. G-banding in a mitotic metaphase showing 46 chromosomes with one small metacentric marker (der15) and two abnormal chromosomes (der12 and derY). Bar = 10 μm

normal 12 and 15 chromosomal pairs were observed. Instead, two derivative chromosomes replaced each one of the missing homologues (Figure 2). The der12 is an inverted 12 with almost a whole long arm of chromosome 15 translocated into it (Figure 2). The abnormal chromosome 15 could not be interpreted until the meiotic and FISH data showed its true identity.

Both parents were karyotypically normal. However, in a single cell from the father, a translocation between chromosomes 12 and 3 was recorded.

AZF microdeletions

Analysis of AZF genes revealed the presence of the three (A, B and C) regions. Thus, no microdeletion of the azoospermia locus in the Yq11 region was shown in this case.

Synaptonemal complex analysis

The analysis of the SCs at pachytene shows 20 autosomal SCs. In all the examined cells, a pentavalent and a univalent chromosome (frequently associated with the multivalent chromosome) are present (Figure 3). Thus, a complex rearrangement is present in spermatocytes. Electron micrographs of 20 different spermatocytes were analysed in prints. The pentavalent chromosome has four synapsed ends and two free ends. The special 'excrecences' typical of the human X and Y axes in the normal XY body (Solari, 1980, 1988, 1999) allow the identification of the X axis and a segment of the Y axis. The X chromosome is always a terminal component of the pentavalent chromosome and is associated with another axis through a short SC—which corresponds to the pseudoautosomal region (PAR). At the other end of the pentavalent, the terminal free end is rather short and is followed by the longest SC. This terminal axis is identified as one of the acrocentric chromosomes of the 13–15 group because of its subterminal kinetochore location and the attachment of a nucleolar structure. The other two intermediate SCs are of similar length and should correspond to derivative chromosomes stemming from reciprocal translocations. In many spermatocytes, a small univalent is associated with this pentavalent at the free short end. The pentavalent and the relative lengths of the synaptic regions are shown in a diagram of the pachytene configuration (Figure 4).

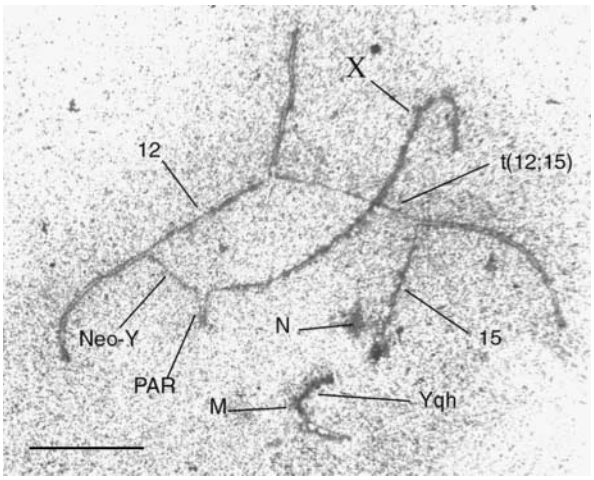

Figure 3. Electron micrograph of the pentavalent + univalent in a microspread spermatocyte. #12 and #15 are the axes of the intact chromosomes 12 and 15. The latter (#15) has an attached nucleolar mass (N) on the non-paired terminus. The neo-Y forms an SC (PAR) with the X axis (X). The X axis has the typical excrescences. One segment (Yqh) of the small marker univalent (M) shows similar excrescences. Bar = 5 μm

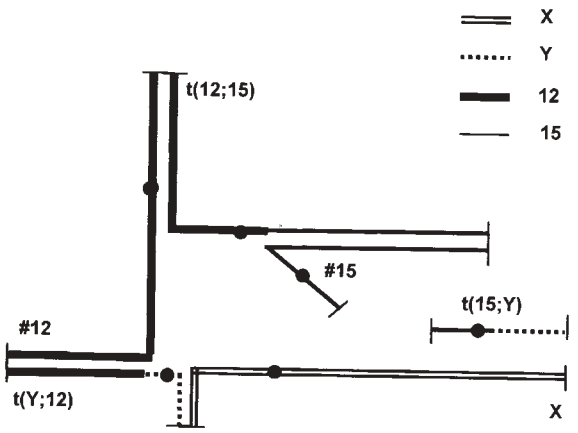

Figure 4. Schematic drawing of the pentavalent. The differentially marked segments represent the mean values of the SCs and axial lengths from a sample of six spermatocytes at pachytene.

Analysis of somatic chromosomes with FISH

On the basis of the previously described data, human probes were selected for FISH in slides from blood cultures.

FISH with the X probe shows that the X chromosome is intact, as it paints only the submetacentric X chromosome and no signal is seen on any other chromosome.

The Y probe paints two chromosomes. One of them is the small marker chromosome that is painted on the heterochromatic arm, which is the same strongly DAPI + arm (Figure 5a–c). The second one is a mid-sized acrocentric chomosome that is painted on the proximal q region including the centromere (Figure 6a). The Y-alphoid DYZ3 repeat probe shows a signal in the centromeric region of this chromosome, and thus it is concluded that this is the chromosome that synapses with the X axis at pachytene through the PAR. Thus, this is a neo-Y chromosome, having the euchromatic part of the normal Y and an autosomal segment (Figure 6b).

The chromosome 12 probe gives signals on three chromosomes: one along the whole of the intact submetacentric chromosome 12, another signal on the long arm of the mid-sized acrocentric neo-Y [t(Y;12)], and the third signal on one arm, including the centromere, of a large metacentric chromosome [der12 or t(12;15)] (Figure 6c). In G-banded karyotypes, it was suggested that an inversion occurred in the der12. FISH with a 12-pter probe gave a signal at the end of the large metacentric, which considering the shapes of the involved chromosomes, would confirm the ocurrence of a pericentromeric inversion (Figure 7).

The chromosome 15 probe gives three signals: one all along the intact acrocentric 15, another on one arm of

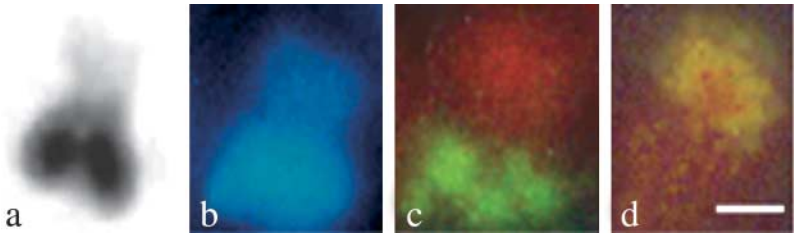

Figure 5. (**a**) C-banding; (**b**) DAPI staining; (**c**) Y chromosome paint; (**d**) chromosome 15 paint of the small marker chromosome. Bar = 1.5 μm.

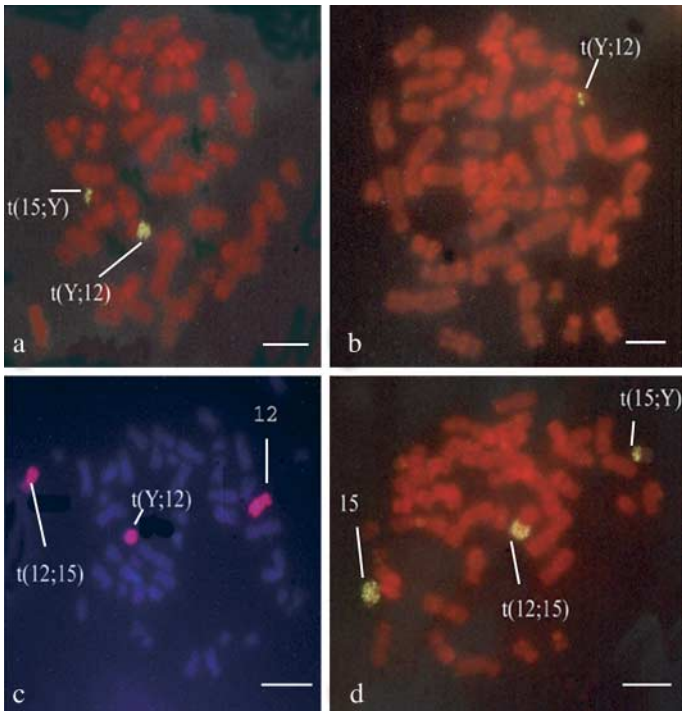

Figure 6. FISH of mitotic lymphocytes with whole chromosome or segmental paints: (**a**) Y chromosome paint; (**b**) Y centromere probe; (**c**) chromosome 12 paint; (**d**) chromosome 15 paint. Bar = 10 μm.

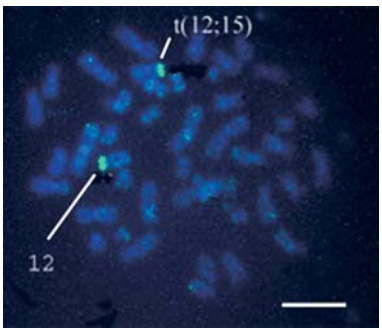

Figure 7. Segmental chromosome painting (FISH) with 12pter. Bar = 10 μm.

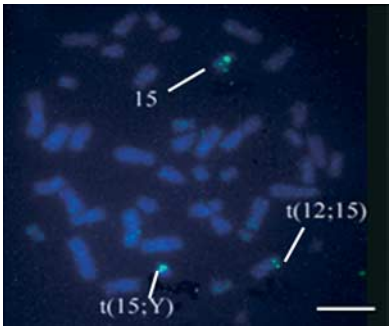

Figure 8. FISH using the Prader–Willi–Angelman probe. One signal is seen in the normal chromosome 15 and the other in the t(12;15)-derived chromosome. A pericentromeric probe for chromosome 15 is also present for identification. Bar = 10 μm.

the large metacentric [der12 or t(12;15)], and the third signal on the small metacentric marker chromosome (Figure 6d). The latter corresponds to the euchromatic arm and, as seen in the corresponding DAPI images (Figure 5d), this probe also paints the corresponding centromeric region. Thus, the marker chromosome t(15;Y) is a der15.

The Prader–Willi–Angelman probe shows one signal in the normal chromosome 15 and the other signal in the t(12;15) derivative chromosome (Figure 8).

Thus the complete propositus karyotype is:
46,X,der(Y;12;15){t(Y;12)q11.23;q21.2);t(inv(12);15){(p11.2q21.2);q13};t(15;Y)(q13;q11.23)}.

Discussion

CCRs are very rare in the human population. Translocations involving three or more chromosomes are thought to lead to a severe reproductive impairment due to meiotic disturbance or unbalanced condition of gametes (Lespinasse *et al.*, 2003). In 50% of all the cases, CCRs are *de novo*, with 25% inherited and 25% of unknown origin. Table I shows the previously studied CCRs in males with normal phenotypes and reproductive impairment. From 12 cases, six consulted because of abortions or malformed newborns and six because of infertility.

In the present work, the seminal analysis revealed azoospermia and the testicular biopsy showed spermatogenic arrest at the spermatocyte level. Cytogenetic studies, analysis of SCs and FISH were performed in this patient because he asked for ICSI treatment. The cytogenetic study of oligo- or azoospermic males prior to ICSI is important because there is a risk of transmission of chromosome aberrations in this group (Tuerlings *et al.*, 1998).

In the present case, the use of the FISH technique was necessary for the correct diagnosis of this CCR, and the analysis of SCs was needed to guide the different FISH steps.

The patient shows the rare occurrence of a neo-Y chromosome, which is the result of a translocation of the euchromatic part of the Y chromosome on the long arm of chromosome 12. The signal of the terminus probe for 12p seen on the terminal region of the abnormal, long metacentric chromosome agrees with the assumption of a previous inversion of chromosome 12. Although in pachytene spreads an inversion loop was not consistently observed, it is known that such loops may rapidly disappear after early pachytene, leading to heterosynapsis. Thus, this complex chromosome rearrangement is apparently balanced and there are three chromosomes with four breakpoints (Figure 9): der(Y) (Ypter-Yq11.23::12q21.2–12qter); der(12)(12pter–12p11.2::12q21.2–12p11.2::15q13–15qter); and der(15)(15-pter–15q13::Yq11.23–Yqter)

The analysis of the pachytene SCs shows that meiotic segregation could not be normal, as there is always a univalent der15, which is the 'marker chromosome' in light microscopy of somatic metaphases. The primary infertility is due to an arrest of spermatogenesis at the spermatocyte level, mainly at late pachytene. As no sperm were found in seminal analysis or in histological studies, it is concluded that the few spermatocytes that escape pachytene apoptosis are unable to deal with a pentavalent and one univalent in the metaphase I spindle and die before anaphase I.

The origin of pachytene apoptosis has been ascribed to a 'pachytene checkpoint' (Roeder and Bailis, 2000) which detects failures in chromosome synapsis and recombination. This checkpoint may lead to pachytene arrest through p53-independent apoptosis (Odorisio *et al.*, 1998). In the present case, the long stretches of asynaptic regions in the pentavalent plus univalent at pachytene could initiate the apoptotic process. A further deleterious factor is the involvement of the sex chromosomes in this aberration and the close attachment of the autosomal regions of the pentavalent to the inactive X chromosome. The typical transcriptional silencing of the XY body in normal men (Solari, 1999) may spread to close, autosomal chromatin (Jaafar *et al.*, 1993; Solari, 1999), leading to the lack of transcripts necessary for completion of meiosis. The mechanisms of meiotic sex chromosome inactivation (MSCI) are presently unknown.

In this patient, the normal phenotype suggests that the breakpoints in Yq11.23, 12p11.2, 12q21.2 and 15q13 do not inactivate functional genes. The breakpoints may not include genes or gene regions with regulatory functions, whose disruption could produce phenotypic alterations. However, other disruptions at the molecular level cannot be disregarded.

The origin of CCRs is unknown. Exposure to ionizing radiation or the administration of immunosupressive drugs

Table I. Published cases of complex chromosomal rearrangements in males with normal phenotype and fertlity disturbances

No.	Origin	Phenotype	Involved chromosomes	Breakpoints	References
1	*De novo*	Infertility	4, 7, 15	4q24, 7q22,15q24	Chandley *et al.* (1975)
2	Unknown	Infertility	11, 12, 21	11q22, 12q13, 21p11	Joseph and Thomas (1982)
3	*De novo*	Malformations	9, 10, 18	9p24, 10q24, 18q21	Bourrouillou *et al.* (1983)
4	Unknown	Infertility	2, 4, 9	2p13, 4q25, 9p12	Saadalhah and Hulten (1985)
5	*De novo*	Infertility	1, 5, 10, 12	1q42, 5p13, 10q24, 12q24	Rodríguez *et al.* (1985)
6	Familial	Spontaneous abortions	7, 8, 9	7q21, 7q33, 8p23, 9p23	Walker *et al.* (1985)
7	Familial	Spontaneous abortions	3, 4, 6	3q12, 3q25, 4q33, 6q13	Gorski *et al.* (1988)
8	Familial	Spontaneous abortions	9, 12, 13	9q22, 12q22, 13q32	Johannisson *et al.* (1988)
9	Unknown	Infertility	7, 9, 13	7p14, 9p11.2, 13p21, 13q21	Siffroi *et al.* (1997)
10	*De novo*	Malformations	6, 7, 18, 21	6q22, 6q25, 7q21.3, 7q32.1, 18p11.2, 18q21.3, 21q21.3	Rothlisberger *et al.* (1999)
11	*De novo*	Malformations/abortions	7, 8, 9	7q22, 7q32, 8q21.2, 9p24	Cai *et al.* (2001)
12	*De novo*	Infertility	Y,12,15	Yq11.23, 12p11.2, 12q21.2, 15q13	This study

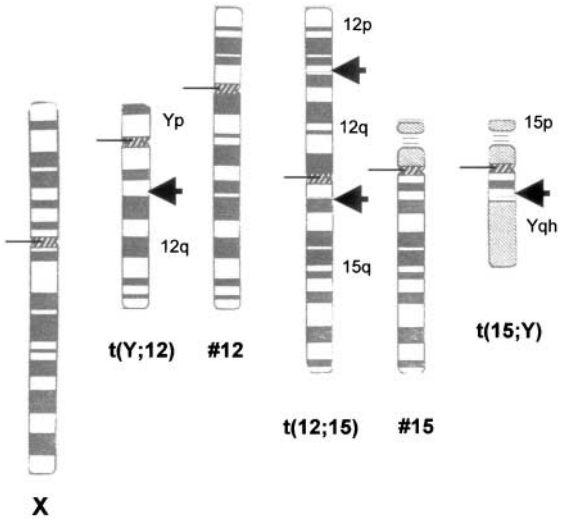

Figure 9. Breakpoint locations on the three chromosomes involved in the present CCR.

before or during pregnancy (Lucas *et al.*, 1992), advanced paternal age (Benzacken *et al.*, 1998) and a possible instability of maternal chromosomes (Kousseff *et al.*, 1987) have been suggested as possible factors in the origin of CCRs.

In the present case, the paternal origin of the complex is evidenced by the presence of the Y-derived elements, and this paternal origin agrees with the previously recorded 11 cases of '*de novo*' CCRs. The literature shows that this is the second case of CCRs where the Y chromosome is involved. The other case (Joyce *et al.*, 1999) was detected in a child with multiple congenital anomalies.

The scarce number of cases with male transmission were detected due to subfertility, oligospermia or azoospermia, as documented in the literature (Chandley *et al.*, 1975; Joseph and Thomas, 1982; Rodriguez *et al.*, 1985; Saadallah and Hulten, 1985). Male carriers of CCRs may not be sterile, and the transmisssion of CCRs has been documented (Meer *et al.*, 1981; Bourrouillou *et al.*, 1983; Walker *et al.*, 1985; Gorski *et al.*, 1986; Schmidt and Passarge, 1988). The genetic, reproductive risk of the CCR carriers depends on the involved chromosomes and the sites of breakpoints. The distribution of specific breakpoints is non-random, and frequent sites are located at 1q25, 4q13, 6q27, 7p14, 9q12, 11p11, 12q21, 13q31 and 18q21 (Gorski *et al.*, 1988). In general, the risk of spontaneous abortions is 48.3%, and 18.4% of all live births from CCR carriers resulted in phenotypically abnormal offspring (Gorski *et al.*, 1988; Lespinasse *et al.*, 2003).

In the present case, the theoretical origin of the CCR is interpreted as an initial inversion of chromosome 12 (at the breakpoints 12p11.2::12q21.2). The inverted 12 was translocated with chromosome 15, resulting in two derivative chromosomes, one of which is then involved in a further interchange with the Y chromosome (see Results). The scheme (Figure 10) shows the possible paths in the production of this CCR.

In conclusion, the presence of CCRs in subfertile men may be tested more efficiently through the combined use of SC

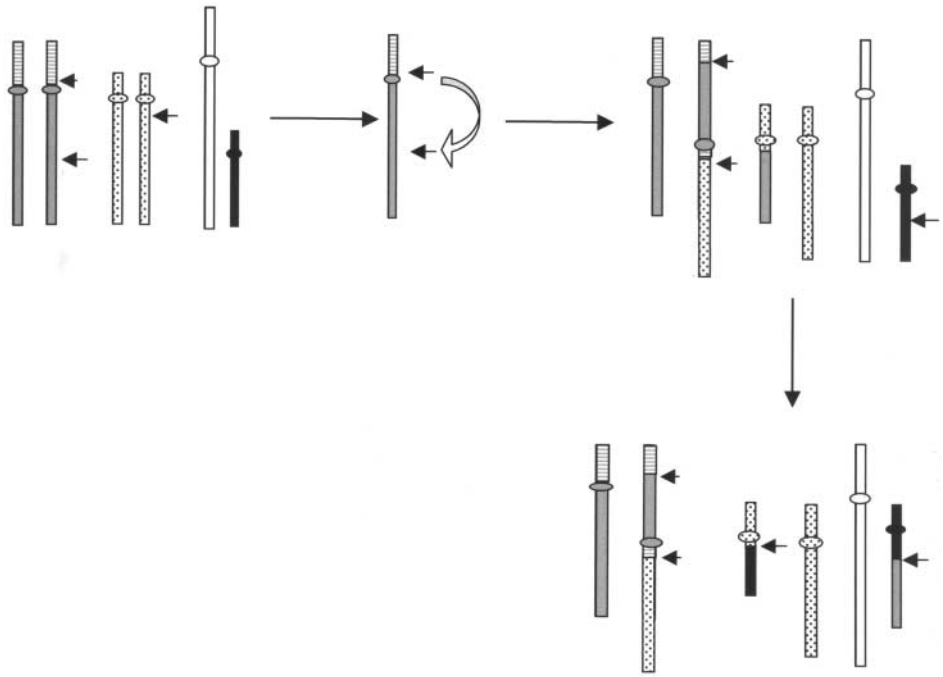

Figure 10. Possible origin of the elements of the CCR in the present patient. The involved chromosomes are Y, 12 and 15. A translocation between the inverted chromosome 12 and chromosome 15 forms a metacentric chromosome (der12), which pairs at pachytene with both the intact 15 and the intact 12. The other derivative chromosome is the neo-Y or der(Y), which is formed by the centromeric region of the Y and by Yp. This der(Y) also has a region of 12q, thus pairing at pachytene with the intact chromosome 12. The X chromosome pairs through its PAR with the neo-Y. The marker chromosome der(15) (a small metacentric), is frequently near the original chromosome 15 at one end of the pentavalent. Colour code: Y = black; X = white; 12 = grey; 15 = segments with points; 12p = striped grey.

analysis and FISH methods, but the meiotic outcome is variable. The worst prognosis for spermatogenesis completion occurs when the aberrations include the sex chromosomes and thus there is a possible spreading of MSCI, as shown in the present case. This phenomenon (MSCI) should be taken into account in human cases of spermatogenic arrest.

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