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Alternative centromeric inactivation in a pseudodicentric t(Y;13)(q12;p11.2) translocation chromosome associated with extreme oligozoospermia

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EDITOR—Centromeres are the specialised regions of chromosomes that ensure normal transmission of sister chromatids to each daughter cell after mitosis. Alphoid satellite DNA sequences, consisting of tandemly repeated

≈170 bp units present at all human centromeres, contain the information necessary for centromeric function,¹ despite the observation of marker chromosomes lacking detectable alphoid DNA.²⁻⁴ Dicentric chromosomes, resulting from

some Robertsonian or Y;autosome translocations, represent a valuable tool for studying factors which ensure that only one of the centromeres is mitotically active, thus preventing chromosomal bridges and breakages to occur at anaphase. It has been shown that centromeric inactivation is largely an epigenetic event⁵ based on the ability of alphoid sequences to bind specific centromeric proteins (CENPs), particularly the CENP-C protein which is necessary for proper kinetochore assembly.⁶

Here we describe a de novo dicentric Y;13 (q12;p11) translocation chromosome found in a severely oligozoospermic patient and exhibiting a variable pattern of centromeric activity, as defined by the localisation of the primary constriction.

Methods and results

This patient was a healthy, 20 year old, West Indian man who referred himself to the laboratory because of ejaculation problems. Sperm analysis showed first an abnormal viscosity of ejaculate which took as long as six hours to liquefy and, second, an extreme oligozoospermia at 0.1 million spermatozoa/ml. Biochemical parameters of the semen were normal. Further sperm counts showed a similar constitution of ejaculate and testicular impairment varying from severe oligozoospermia to azoospermia or cryptozoospermia. Testicular biopsy was not proposed.

Karyotyping was performed on blood lymphocytes by conventional cytogenetic methods using R and G banding and BrdU incorporation after cell culture synchronisation. It showed an apparently balanced reciprocal translocation between the distal region of the Y chromosome long arm and the short arm of one chromosome 13. Paternal chromosomes were normal.

Curiously, this abnormal chromosome exhibited two different features with regard to the position of its primary constriction. In 50 cells analysed, this was localised at the Y centromere in about half the cells, giving a characteristic aspect of a large acrocentric chromosome, and at the chromosome 13 centromere in others, leading to an abnormal metacentric rearranged chromosome (fig 1). On the basis of these morphological data, the translocated chromosome was considered as pseudodicentric. C banding indicated that Y heterochromatin was apparently preserved and included chromosome 13 centromere labelling while the Y centromere was normally present (fig 1). Silver staining failed to detect any nucleolar organiser region (NOR) on the translocated chromosome (data not shown). Fluorescence in situ hybridisation (FISH), using Y and chromosome 13 specific probes, confirmed cytogenetic results (data not shown). Thus, chromosomal breakpoints were localised in Yq12 and 13p11.2 and the proband's karyotype was 45,X,-13,-Y,+psu dic(Y),t(Y;13)(q12;p11.2) [27]/45,X,-13,-Y,+psu dic(13),t(13;Y)(p11.2;q12) [23]. No normal cell line was observed.

After genomic DNA extraction, PCR reactions were performed for checking the integrity

Figure 1 Partial view of proband's karyotype after R banding (A, B, D) and C banding (C, E) showing the variable aspect of the translocation chromosome according to centromeric activation (arrows). (A) Normal chromosome 13. (B) Translocation chromosome with the Y chromosome active centromere giving a large acrocentric abnormal chromosome. (C) View after C banding. (D) Chromosome 13 active centromere leading to a metacentric translocation chromosome. (E) View after C banding.

of the Y chromosome euchromatic region. Twelve different STSs (sequence tagged sites), corresponding to the three AZF loci (azoospermia factor, *AZF*a: sY85, sY95; *AZF*b: sY114, sY116, sY125, sY127; *AZF*c: sY135, sY149, sY152, sY254), to SRY (sY14), and to the heterochromatic distal Yq region (sY160), were amplified and gave positive results in the proband's DNA samples, indicating the absence of interstitial microdeletion (data not shown).

Because the distal part of the Y chromosome long arm is difficult to analyse by conventional cytogenetic techniques, both molecular and FISH approaches were used for a better characterisation of the chromosomal breakpoints. However, FISH alone could give positive results if this breakpoint was localised within the region recognised by the probe. A molecular polymorphic marker (DXYS154), corresponding to the pseudoautosomal region 2 (PAR2), localised at the tip of sex chromosome long arms, as well as two autosomal markers (D7S1779 and D14S983), were amplified both in our patient and his father and compared with each other (maternal blood sample was not available). These three markers are dinucleotide repeats, (CA)_n, and were amplified by PCR, separated on a 6% polyacrylamide/urea gel, then transferred to a nylon membrane, and hybridised to a labelled GT probe (ECLTM, Amersham Pharmacia Biotech). Results showed that the proband received a copy of one of each autosomal markers from his father and only one copy of the DXYS154 marker, which was different in size from the paternal one (fig 2A), thus indicating the lack of PAR2 on the abnormal Y chromosome. This was confirmed by FISH using a cosmid probe of this region which indicated that only the X chromosome exhibited a fluorescent signal in our patient whereas both gonosomes were labelled in paternal metaphases (fig 2B, C). Therefore, the translocation breakpoint in the Y chromosome was localised in the distal part of the heterochromatic region (DYZ1).

Functional activity of one or both centromeres was investigated using an antibody against the kinetochore associated protein CENP-C (a gift from Professor W C Earnshaw, University of Edinburgh, Scotland). For this purpose, freshly prepared chromosomes

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Figure 2 Molecular characterisation of the translocation breakpoint. (A) (a) Amplification of a polymorphic marker localised in PAR2 in the father (F) and proband (P). Two bands corresponding to X and Y chromosomes were present in the father's DNA while only the maternal copy of a different size was amplified from the proband's DNA, thus indicating the lack of PAR2 on his Y chromosome. (b, c) Amplification of autosomal polymorphic markers. The proband received a paternal copy of each marker. (B, C) Localisation of chromosomal breakpoints by FISH using a cosmid probe coding for the PAR2 region. Both gonosomes were labelled at the tip of their long arm in paternal metaphases (B, thick arrows) whereas, in the proband, only the X chromosome exhibited a fluorescent signal (C, thin arrow). Arrowhead indicates the unlabelled translocation chromosome).

were first hybridised with a Y centromeric fluorescent probe (Oncor, USA), labelled with rhodamine, and observed under UV light for identifying precisely the Y chromosome in mitosis and the position of its primary constriction. The localisation of each mitosis observed was then carefully recorded. After several washes in PBS and TEEN buffer (0.2 mmol/l EDTA, 25 mmol/l NaCl, 1.0 mmol/l triethanolamine, 0.5 % Triton, 0.1 % BSA), slides were allowed to incubate with the rabbit anti-CENP-C antibody, diluted 1/1000, for one hour at room temperature. They were then rinsed three times in KB buffer (10 mmol/l Tris HCl, pH 7.7, 150 mmol/l NaCl, 0.1% BSA)

and incubated with a biotinylated goat anti-rabbit Ig, diluted 1/500, for 30 minutes at 37°C. After washing in KB buffer, immunolabelling was performed by incubating slides with FITC conjugated avidin. Mitoses, which had been studied by FISH, were reanalysed and immunolabelling of CENP-C was compared to the position of the primary constriction. This method was reliable and led to a slight decrease of immunolabelling intensity.

The results showed clearly that protein CENP-C labelling is exclusively localised at the site of the primary constriction in the rearranged chromosome, thus indicating a variable activation of one of the centromeres in the proband's cells (fig 3).

Discussion

Apparently balanced Y;autosome translocations can be found either in fertile^{7,8} or infertile^{9,10} patients with, in some cases, phenotypic differences between carriers of the same translocation in a family.^{11,12} Usually, infertility is the consequence of a Y chromosome breakpoint occurring in the euchromatic long arm segment and leading to the loss of genes implicated in the azoospermia factor (AZF). However, in cases with an apparently intact Y chromosome translocated onto an autosome, spermatogenic impairment is thought to result from abnormal meiotic behaviour of translocated chromosomes, which interact with the XY body in most germ cells.¹⁰ Spreading of X chromosome inactivation to autosomal segments or an abnormal sex vesicle constitution are the main explanations for meiotic failure and spermatocyte degeneration. In our case, the Y chromosome breakpoint was localised at the end of the heterochromatic region and integrity of the euchromatic long arm segment was ascertained by molecular analysis. Therefore, despite the lack of testicular biopsy in our patient, oligozoospermia was probably the consequence of these meiotic events, although it was not possible to explain the abnormal constitution of his semen. Loss of PAR2, which is observed in infertile men carrying a Y chromosome terminal deletion but not in those with an interstitial one, is unlikely to be responsible for impairment of spermatogenesis in our patient.

More interesting was the variable nature of the translocated chromosome in relation to the position of its primary constriction. Such a polymorphism is very rarely found during cytogenetic investigations but a case similar to ours has already been described in a child with congenital malformations owing to the existence of an additional isochromosome 13q in 23% of cells in blood and 5% in skin.¹³ Variable centromeric activity has also been observed in an infertile patient carrying a t(Y;14) translocation chromosome.¹⁴

However, the occurrence of dicentric chromosomes is a common event in Robertsonian translocations, whole arm reciprocal translocations, or in structurally abnormal chromosomes like isochromosomes. Mitotic stability of such chromosomes implies that only one centromere is active, which has been related to

Figure 3 Binding of CENP-C protein to the active centromere. The translocation chromosome was identified by DAPI staining and FISH with a Y centromeric probe showing either two well separated fluorescent spots or a more compact signal according to chromosome 13 (top) or Y (bottom) centromere activation. Labelling with an antibody to CENP-C (right) was always localised at the site of the primary constriction on the rearranged chromosome (white arrows).

the specific binding of the centromeric protein CENP-C at this site.¹⁵ Indeed, while inactive centromeres retain their ability to bind some centromeric proteins like CENP-B, kinetochore assembly and centromeric activation require at least CENP-C and/or CENP-E binding.¹⁶ Molecular analysis of a de novo dicentric Y;21 translocation chromosome, with several clones exhibiting variable patterns of centromeric activation like our case, has shown multiple forms of alphoid DNA deletions of the Y centromere.⁵ However, in this latter case, deletions were not systematically associated with Y centromeric inactivation. These results indicate that the centromeric activation/inactivation process is largely dependent on epigenetic factors but that it can occasionally be associated with changes in alphoid DNA structure.

The physical distance between the two centromeres in a dicentric chromosome may be an additional factor for predisposing cells to inactivate one of the centromeric structures. Dicentric Xq chromosomes, in which centromeres were separated by 4–12 Mb of Xp material, have been shown to bind CENP-C on both centromeres in most cells and, therefore, to

present a high degree of coordination between the two sets of active kinetochores at mitosis.¹⁷ Such mitotic behaviour differs from that observed in dicentric X chromosomes with well separated centromeres, by 34 Mb or more, in which one of them is systematically inactivated.¹⁷ However, in these cases, the symmetrical appearance of the abnormal chromosomes did not allow the authors to determine if the inactivation process always occurred at the same centromere or alternately at one or the other.

The same question arises from the analysis of dicentric chromosomes in which centromeres are very close together. This may be the case in some autosomal translocation chromosomes like those involving acrocentric pairs. Mitotic instability generated by the activation of both centromeres would lead to the loss of autosomes and to the death of the abnormal cell lines in which such an event occurred. The surviving clones would be only those in which one centromere has been inactivated regardless of its nature and the fact that it may be always the same one or not. Indeed, the centromere vicinity makes a possible alternative inactivation of one of them indistinguishable by current cytogenetic methods and immunochemical techniques. Only dicentric translocation chromosomes with a non-symmetrical appearance and distant centromeres, like that of our patient, would allow an alternative inactivation process to be diagnosed.

In conclusion, the case described here emphasises the close relationship between structural chromosomal rearrangements, especially those involving the Y chromosome, and male infertility. Moreover, it underlines an epigenetic mechanism of alternative centromeric inactivation which may be a common phenomenon in dicentric chromosomes.

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