Unbalanced 1q Whole-Arm Translocation Resulting in der(14)t(1;14)(q11–12;p11) in Myelodysplastic Syndrome

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Key Words

Centromere • FISH • Myelodysplasia • 1q Whole-arm translocation

Abstract

Unbalanced whole-arm translocations (WATs) of the long arm of chromosome 1, resulting in complete trisomy 1q, are chromosomal abnormalities detectable in both solid tumors and hematologic neoplasms. Among the WATs of 1q to acrocentric chromosomes, a few patients with der(1;15) described as a dicentric chromosome have been reported so far, whereas cases of der(1;14) are much rarer. We report on a case of der(1;14) detected as single anomaly in a patient with myelodysplastic syndrome. The aim of our work was to investigate the breakpoints of the (1;14) translocation leading to the der(1;14). Fluorescence in situ hybridization (FISH) experiments have been performed on chromosome preparations from bone marrow aspirate, using specific centromeric probes of both chromosomes, as well as a probe mapping to 1q11 band. FISH results showed that in our patient the derivative chromosome was monocentric with a unique centromere derived from chromosome 14. The breakpoints of the translocation were located in the short arm of chromosome 14 and in the long arm of chromosome 1, between the

alphoid D1Z5 and the satellite II domains. The 1q breakpoint was within the pericentromeric region of chromosome 1, which is notoriously an unstable chromosomal region, involved in different chromosomal rearrangements.

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Trisomies of the long arm of chromosome 1, resulting from different chromosomal rearrangements, including tandem duplications as well as unbalanced, jumping and whole-arm translocations (WATs) of 1q, may be found in both solid tumors and hematologic disorders. Cases of solid tumors include Wilms' tumor [Kaneko et al., 1983] and hepatoblastoma [Parada et al., 2000; Tomlison et al., 2005], while, among hematologic disorders, cases of myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), chronic myelomonocytic leukemia and multiple myeloma (MM) have been reported [Mecucci et al., 1985; Alitalo et al., 1989; Fonatsch et al., 1991; Djordjević et al., 2008; Mitelman et al., 2011].

Unbalanced WATs of 1q are chromosomal aberrations which may involve different chromosomes [Mitelman et al., 2011]. The derivatives of these translocations have been shown to be dicentric in few cases of der(1;7) [Alitalo et al., 1989; Wang et al., 2003] and der(1;15) [Wong

Fig. 1. G-banded karyotype. The arrow indicates the der(1;14).

et al., 1995; Michaux et al., 1996]. Very few data are available about der(1;14), which is a much rarer chromosomal rearrangement [Busson-Le Coniat et al., 1999; Djordjević et al., 2005]. Here we report on the findings of fluorescence in situ hybridization (FISH) studies performed in a patient with MDS showing this unusual translocation.

Materials and Methods

Case Report

The patient is a 72-year-old female, diagnosed with bone marrow aplasia in 1996, at 56 years. After a treatment with antilymphocytic globulin, cyclosporin A and testosterone she achieved complete remission which lasted until March 2004, when she came to our attention because of pancytopenia, slight splenomegaly and low-grade fever. Blood counts showed: hemoglobin 7.6 g/l, white blood cells $1.5 \times 10^9/l$, platelets $110 \times 10^9/l$. Bone marrow was hypocellular and showed signs of dysplasia involving more than 10% of the myeloid, erythroid and megakaryocytic lineage. Therefore, the diagnosis was refractory cytopenia with multilineage dysplasia according to the WHO classification [Swerdlow et al., 2008]. The patient was offered a treatment with erythropoietin plus standard supportive measures. Follow-up bone marrow evaluations showed a substantially stable morphological picture. In 2006 she also developed a systemic sarcoidosis which was satisfactorily controlled by a high-dose steroid treatment. At present the patient's conditions are good, without signs of evolution to AML. The first cytogenetic analyses, performed at the time of the diagnosis of marrow aplasia and during the long-lasting stationary phase of the disease, showed normal karyotype, thus making more likely that the chromosomal change observed during the evolution to MDS is therapy-related.

Cytogenetic and FISH Studies

Standard procedures were used for routine cytogenetics. Metaphases obtained from unstimulated bone marrow cells were analyzed in GTG- or QFQ-banding after 24/48-hour culture.

FISH studies were performed using the following commercial probes: whole chromosome painting probes of chromosomes 1 and 14 (wcp1, wcp14), centromeric probes of chromosome 1 (locus D1Z5 and satellite II/III (SAT II/III)), all supplied by Abbott Molecular/Vysis (Des Plaines, Ill., USA) and Alphoid probe 14/22 (locus D14Z1/D22Z1), supplied by Cytocell Ltd (Cambridge, UK). The slides for FISH were prepared according to standard procedures and subsequently co-denatured together with the probes at 73°C for 2 min using the Vysis Hybrite Hybridization System (Downers Grove, Ill., USA). Afterwards, they were incubated overnight at 37–42°C and detected according to the suppliers' instructions. The slides were then stained with DAPI and observed with Olympus BX61 fluorescence microscope using suitable filters.

Results

Both analyses on bone marrow blood were performed in 1996, when the patient was diagnosed with bone marrow aplasia, and in 2004 during follow-up, normal karyotype in all the examined cells was shown.

The first analyses on bone marrow blood were performed in 1996, when the patient was diagnosed with bone marrow aplasia, and in 2004 during follow-up, and normal karyotype in all the examined cells was shown. These analyses were performed by another cytogenetic laboratory, and therefore data about the number of screened cells are unavailable.

Fig. 2. FISH with wcp(1) (green) and wcp(14) (red). The arrow indicates the der(1;14).

Fig. 3. FISH with CEP(1) (red) and CEP(14) (green). The der(1;14) indicated by an arrow shows a green spot only.

Table 1. Cytogenetic and clinical data of the present case

Year	Cytogenetics	Diagnosis	Therapy
1996	46,XX	bone marrow aplasia	antilymphocytic globulin, cyclosporin, testosterone
2004	46,XX	RCMD	erythropoietin, standard supportive therapies
2005	46,XX,der(14)t(1;14)(q11-12;p11)[11]/46,XX[14]	RCMD	standard supportive therapies
2006	46,XX,der(14)t(1;14)(q11-12;p11)[7]	RCMD + systemic sarcoidosis	standard supportive therapies + high-dose steroid treatment
2010	46,XX,der(14)t(1;14)(q11-12;p11)[22]/46,XX[3]	RCMD	standard supportive therapies
2011	46,XX,der(14)t(1;14)(q11-12;p11)[15]/46,XX[5]	RCMD	standard supportive therapies

RCMD = Refractory cytopenia with multilineage dysplasia.

In 2005, the patient was admitted to the hematologic unit of our university. At that time, a standard cytogenetic analysis showed a mosaic of normal and pathological cells with a ratio of 14:11 between normal and abnormal cells. In the pathological clone 1 chromosome 14 was replaced by a rearranged chromosome, seemingly consisting of the long arm of chromosome 1 and the long arm of chromosome 14 (fig. 1). This interpretation was confirmed by FISH experiments with wcp probes of chromosomes 1 and 14 (fig. 2). The derivative chromosome, identified as der(1;14), was positive for the alphoid-specific probe CEP(14/22) and negative for the alpha satellite probe of chromosome 1 (locus D1Z5) (fig. 3). The probe corresponding to the SAT II/III region of chromo-

some 1 gave a positive signal on der(1;14) (not shown). These findings clearly indicated that the translocation breakpoint on chromosome 1 was located between the D1Z5 and SAT II/III locus, so sparing the centromeric alphoid block, while the chromosome 14 had a breakpoint on its short arm, retaining its own centromere. The complete karyotype of the abnormal clone, according to the International System for Human Cytogenetic Nomenclature [ISCN, 2009], was: 46,XX,der(14)t(1;14)(q11-12;p11).ish der(14)(wcp1+,SAT II/III+,D1Z5-,D14Z1/D22Z1+,wcp14+). Subsequent analyses, performed in February 2006, March 2010 and February 2011, confirmed the persistence of the abnormal clone (table 1).

Table 2. Reported cases with centromere translocations involving 1p10 or 1q10 [Mitelman et al., 2011]

Chromosome change	Total	Non-hemato- logic neoplasia	Hematologic malignancies	MDS/AML	ALL/CLL/ lymphoma	CMPD	MM/plasma cell leukemia
der(1;2)(p10 or q10;p10 or q10)	12	8	4	1			3
der(1;3)(p10 or q10;p10 or q10)	18	17	1	1			
der(1;4)(p10 or q10;p10 or q10)	5	3	2				2
der(1;5)(p10 or q10;p10 or q10)	15	7	8		3		5
der(1;6)(p10 or q10;p10 or q10)	18	11	7		4		3
der(1;7)(p10 or q10;p10 or q10)	271	11	259	218	9	25	8
der(1;8)(p10 or q10;p10 or q10)	16	9	7		1		6
der(1;9)(p10 or q10;p10 or q10)	19	7	12	1	5	1	5
der(1;10)(p10 or q10;p10 or q10)	3	2	1	1			
der(1;11)(p10 or q10;p10 or q10)	12	10	2		1		1
der(1;12)(p10 or q10;p10 or q10)	5	1	4		4		
der(1;13)(p10 or q10;p10 or q10)	29	11	18	4	8	3	3
der(1;14)(p10 or q10;p10 or q10)	26	10	16	6	4	4	2
der(1;15)(p10 or q10;p10 or q10)	43	10	33	6	12	7	8
der(1;16)(p10 or q10;p10 or q10)	125	67	58	5	3	1	49
der(1;17)(p10 or q10;p10 or q10)	15	5	10	3	4	1	2
der(1;18)(p10 or q10;p10 or q10)	6	1	5	2		2	1
der(1;19)(p10 or q10;p10 or q10)	22	9	13		1		12
der(1;20)(p10 or q10;p10 or q10)	2			1	1		
der(1;21)(p10 or q10;p10 or q10)	21	9	12	3	3	2	4
der(1;22)(p10 or q10;p10 or q10)	12	6	6	1	1		4

ALL = Acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphoblastic leukemia; CMPD = chronic myeloproliferative disease; MDS = myelodysplastic syndrome; MM = multiple myeloma.

Discussion

Unbalanced WATs of chromosome 1q, which involve centromeric or pericentromeric regions of different chromosomes, differ from the typical balanced reciprocal translocations. In fact the abnormal clone retains 2 copies of an apparently normal chromosome 1 and only 1 out of the 2 possible derivatives, resulting in complete trisomy 1q, associated with partial monosomy of the partner chromosome. As reported in table 2, the extra 1q may be fused with different recipient chromosomes, but some rearrangements, such as der(1;7), der(1;16) and der(1;15), seem to recur in different hematological malignancies [Mitelman et al., 2011]. In particular, der(1;7), which is the most frequent WAT of 1q, is non-randomly distributed among neoplastic hematological diseases, with a large prevalence in MDS/AML. The der(1;16) is the second most frequent 1q WAT and is prevalent in MM. Other 1q rearrangements seem to be randomly shared among solid and hematological tumors, among which myeloid

and lymphoid neoplasms are nearly equally involved. These differences could reflect the effects of the concomitant partial aneuploidy of the partner chromosome, which always occurs in this peculiar chromosomal rearrangement, namely monosomy 7q in der(1;7) and monosomy 16p in der(1;16). Another not less relevant aspect is that the derivative chromosome 1 is not often a single anomaly but is part of complex karyotypes.

The molecular mechanism of translocations involving the entire q arm of chromosome 1 has been exhaustively investigated by Alitalo et al. [1989] and Wang et al. [2003] on several patients with der(1;7). These authors showed that the derivative chromosome contains 4 alphoid subsets, 2 from chromosome 1 and 2 from chromosome 7. They also demonstrated that the breakpoints on chromosome 1 are randomly distributed in different patients inside the alphoid block D1Z7. Therefore, the (1;7) translocation indicated as der(1;7)(q10;p10) or (q10;q10) gives rise to a dicentric chromosome.

Table 3. Cases with der(1;14) according to Mitelman et al. [2011] and present case

Author	Age/ sex	Disease	Karyotype	Previous exposure to toxic agents	Survival
Swolin et al., 1986	59/M	post PV MDS	46,XY,+1,der(1;14)(q10;q10)	busulfan	6 months after MDS
Ben-Neriah et al., 1991	1/M	bilineage leukemia	47,XY,-14,+der(14)t(1;14)(q11;p11),+22	aracytin, daunomycin, etoposide	1 year
Nylund et al., 1994	28/F	ALL/LL	46,XX,+1,der(1;14)(q10;q10),der(19)t(1;19)(q23;p13)	de novo	
Hashimoto et al., 1995	54/M	NHL	47,XY,+X[6]/35-42,XY,der(1;14)(q10;q10),der(1;14)(p10;q10)[cp4]/46,XY[11]	de novo	
Uckun et al., 1998	?/F	ALL	46,XX,t(1;19)(q23;p13),der(14)t(1;14)(q11;p11)		
Busson-Le Coniat et al., 1999	65/M	PV	47,XY,der(14)t(1;14)(q11;p11)		
Schoch et al., 2001	49/F	acute monoblasti leukemia FAB M5A	46,XX,+i(5)(p10),+8,der(14)t(1;14)(q11;p11)		
Chan et al., 2003	59/F	Burkitt/leukemia	47,X,add(X)(p22),+7,t(8;14)(q24;q32)[2]/47,idem,add(7)(p22)[5]/47,idem,+1,der(1;14)(q10;q10)[42]/47,idem,+1,der(1;14)(q10;q10)[2]		
Andrieux et al., 2003	64/F	post PV MF	46,XX,der(1;14)t(1;14)(q10;p10)	pipobroman	2 years after PPMF
Harrison et al., 2003	?/M	MM	46,X,-Y,dic(1;6)(q10;q15) × 2,der(4)t(4;14)(p16;q32),der(8)t(8;13)(q24;q14) × 2,der(13)t(8;13)(q24;q14)dup(13)(q14.3q14.3),-13,der(1;14)(q10;q10)t(4;14)(p16;q32),dic(1;17)(q10;q25)[7]		
Imashuku et al., 2003	11/F	RAEB	46,XX,+1,der(1;14)(q10;q10)/46,idem,add(9)(q34),add(17)(p11)		
Harada et al., 2004	69/M	secondary MDS/ RAEBt	46,XY,del(12)(p12),der(14)t(1;14)(p10;p10)	atomic bomb exposure	
Zamora et al., 2004	?/F	PV	46,XX,der(14)t(1;14)(q10;q10)[8]/46,XX[12]	de novo	
Barouk-Simonet et al., 2005	73/M	RARS	45-46,der(1;14)(p10;q10),del(5)(q13;q33),+8,+9,del(11)(q14),del(20)(q11),der(21)t(21;21)(?,?)ish(AML1-;BCR+),-22[cp]		
Keller et al., 2006	68/F	NHL	51,XX,+X,+2,in(3)(q26q27),+12,t(14;18)(q32;q21),der(14)t(1;14)(q11;p11),+17, dup(17)(q21q25) × 2,+18		
Adeyinka et al., 2007	65/M	ALL	46,XY,+1,der(1;4)(q10;q10)[14]/46,XY[6]		
Adeyinka et al., 2007	73/M	MM	46,XY,+1,der(1;4)(q10;q10)[4]/46,XY[6]		
Adeyinka et al., 2007	74/M	MPD	46,XY,+1,der(1;4)(q10;q10)		
Stamatoullas et al., 2007	30/M	HL	46,X,-Y,del(4)(q28),+8,add(9)(p24),der(14)t(1;14)(q11;p11),der(21)t(1;21)(q11;p11)		
Douet-Guilbert et al., 2008	51/M	PV	47,XY,+9,der(14)t(1;14)(q11;p11),del(20)(q12)[19]/46,XY[1]		
Lee et al., 2008	10/M	AML M4	46,XY,+1,der(1;14)(q10;q10)	de novo	
Djordjević et al., 2008	43/M	CMML	46,XY,+1,der(1;14)(q10;q10)	de novo	
Millington et al., 2008	79/F	MDS	46,XX,der(14)t(1;14)(q11;p13)[14]/46,XX[6]	de novo	1 year
Present case	65/F	RCMD	46,XX,+1,der(1;14)(q11-12;p11)	antilymphocytic globulin, cyclosporin A, testosterone	

ALL = Acute lymphoblastic leukemia; AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; F = female; HL = Hodgkin lymphoma; LL = lymphoblastic lymphoma; M = male; MF = myelofibrosis; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPD = myeloproliferative disease; NHL = non-Hodgkin lymphoma; PV = polycythemia vera; PPMF = myelofibrosis after polycythemia vera; RAEB = refractory anemia with excess of blasts; RAEBt = refractory anemia with excess of blasts in transformation; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia.

WATs of 1q to acrocentric chromosomes may be interesting to define the role of 1q trisomy in different tumors. In fact, only in cases where the recipient chromosome is an acrocentric and the 1q WAT is present as isolated karyotypic abnormality, the resulting chromosome imbalance may be considered as pure 1q trisomy. Indeed, the loss of the p arm of acrocentric chromosomes is irrelevant, similarly to what occurs in constitutional Robertsonian translocations, which do not seem to have phenotypic effect in normal carriers.

The most common WAT translocation involving an acrocentric chromosome is der(1;15), reported in 33 he-

matologic patients with myeloid and lymphoid malignancies. FISH studies have been performed by Michaux et al. [1996] to investigate the role of centromeric sequences of both chromosomes in the origin of der(1;15). Authors showed the dicentric nature of the der(1;15) chromosome in 1 out of 3 patients reported and they suggested that the preservation of both centromeres could be a constant occurrence in translocation of 1q to chromosome 15.

The unbalanced translocation leading to der(1;14) present in our patient is not a common chromosomal rearrangement. From Mitelman et al. [2011] database we

have collected 23 cases of hematologic patients by using different searching criteria, i.e. karyotype formulae which have apparently the same meaning, such as 'der(14)t(1;14)(q11;p11)', '+1,der(1;14)', 'der(1;14)(p10 or q10;p10 or q10)' or similar. Clinical and cytogenetic data of patients with der(1;14), including ours, are reported in table 3. Among these patients the male sex is prevalent (14:10) and the median age at diagnosis, calculated on 21 patients (data were not available for 3 patients) is 59 years. Over 60% of patients (15/24) had a diagnosis of myeloid disorder, including AML, MDS and myeloproliferative disease, while the remaining patients had acute lymphoblastic leukemia/lymphoma or MM; 5 cases had polycythemia vera or myelofibrosis/MDS after polycythemia vera, in agreement with the high incidence of 1q trisomy already reported in these conditions [Swolin et al., 1986, 2008; Andrieux et al., 2003].

For most patients reported in table 2, information about therapy and survival from diagnosis are incomplete, so that it is really hard to reach any firm conclusion about them.

All but 2 reported cases of der(1;14) have been investigated by standard cytogenetic methods; FISH experiments with centromere-specific probes of chromosomes 1 and 14 are available for 2 patients [Busson-Le Coniat et al., 1999; Djordjević et al., 2005]. Busson-Le Coniat et al. [1999] reported FISH results of 1 patient with polycythemia vera and Djordjević et al. [2005] on 1 patient with chronic myelomonocytic leukemia. In the former, the der(1;14) was negative for the chromosome 1-specific alpha satellite probe D1Z5, while it was positive for a chromosome 1-specific SAT II probe. According to FISH findings, the der(1;14) was interpreted as a monocentric chromosome, with a unique centromere derived from chromosome 14. The breakpoint on 1q was located between the alphoid D1Z5 and the SAT II domain. In the latter case, the der(1;14) was positive for a FISH probe specific for the secondary constriction of 1q (pUC1.77, 1q12–1q21), but no FISH results were available for the alpha satellite-specific probe.

In the present case, FISH findings show that the der(1;14) has a unique centromere derived from chromosome 14, similarly to that observed by Busson-Le Coniat et al. [1999] in their patient. Future studies should further explore whether the mechanism shown as responsible for the occurrence of der(1;14) in our patient is common in 1q WATs to chromosome 14.

Translocations with fusion of 2 chromosome arms, either of homologous or non-homologous chromosomes, produce a derivative chromosome often described as di-

centric, although the translocation breakpoints are mostly unknown.

Most of these centromeric fusions involve chromosomes with large C bands, corresponding to large blocks of constitutive centromeric heterochromatin. They are variable in size in normal individuals, mainly at the centromeres of chromosomes 1, 9, and 16, and are known as common heteromorphisms. Centromeric translocations involving chromosome 1, which result in gain of 1q due to the persistence of 2 apparently normal chromosomes 1, may occur with different mechanisms: a primary duplication of a whole chromosome 1, which precedes the subsequent centromere translocation, or, alternatively, the centromere translocation could precede and perhaps predispose to a subsequent duplication of the entire chromosome 1 [Andersen and Pedersen-Bjergaard, 2000]. Another model suggests a simultaneous WAT and duplication of 1q, subsequent to heterochromatin decondensation, which seems to have a primary role in this rearrangement [Sawyer et al., 1998; Wong et al., 2001].

Centromeric translocations typically do not involve key genes, whose disruption may account for neoplastic proliferation, as observed in several neoplasias, but they usually have as main consequence gain or loss of the entire whole arms of the involved chromosomes. Concerning the unbalanced t(1;14) described in our patient, the main consequence is a genomic imbalance resulting from gain of the long arm of chromosome 1. Trisomies of entire arms are likely implicated in neoplastic processes by a gene dosage effect, analogous to what is reported for numerical aberrations, such as trisomy 8 or other full trisomies. The 1q trisomy implies a deregulation of several genes likely implicated in the control of normal cell cycle kinetics, with a consequent alteration of the balance between proliferation and cell death. Up-regulation of genes mapped to 1q has been shown by gene expression profiling analyses in MM patients with gain of 1q [Shaughnessy et al., 2006], which suggests that gene deregulation could be the main mechanism of tumorigenesis in 1q rearrangements in these patients and likely in other tumors.

Therefore, other mechanisms could be implied, such as heterochromatin-dependent oncogenic mechanisms, as suggested by Fournier et al. [2007]. Constitutive heterochromatin is a specialized compartment within the chromatin and is found primarily at centromeres, telomeres and the pericentromeric regions of certain chromosomes, including chromosome 1. It is composed of gene-poor, repetitive DNA sequences (alpha satellite, SAT II, III) with a pre-eminent role in the control of genome

stability, but it is also relevant for epigenetic control of gene expression through a process termed gene silencing. The involvement of 1q12 SAT II-rich constitutive heterochromatin in several 1q rearrangements suggests that this chromosomal region is absolutely important for initiating and/or progression of different tumors. Our case

highlights that FISH studies with appropriate probes of chromosomal rearrangements involving 1q heterochromatin could be helpful to improve our knowledge about this portion of the human genome, mainly concerning its possible role in the pathogenesis of neoplastic disorders.

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