



p190 bcr-abl rearrangement: a secondary cytogenetic event in some chronic myeloid disorders?

CHRISTOPHE ROUMIER,*^o AGNÈS DAUDIGNON,[#] VALÉRIE SOENEN,*^o BRIGITTE DUPRIEZ,[@]

MARC WETTERWALD,[^] JEAN-LUC LAI,[§] ALAIN COSSON,*^o PIERRE FENAUX,^{***} CLAUDE PREUDHOMME*^o

*Laboratoire d'Hématologie A, Centre Hospitalier Universitaire of Lille; ^oUnité Inserm 524, Lille; [#]Laboratoire de cytogénétique, Centre Hospitalier of Valenciennes; [@]Service des Maladies du Sang, Centre Hospitalier of Lens; [^]Service de Médecine Interne, Centre Hospitalier of Dunkerque; [§]Laboratoire de cytogénétique, Centre Hospitalier Universitaire of Lille; ^{***}Service des Maladies du Sang, Centre Hospitalier Universitaire of Lille, France

ABSTRACT

Background and Objectives. A small number of chronic myeloproliferative disorders with hematologic features of chronic myelomonocytic leukemia (CMML) or atypical chronic myeloid leukemia and Ph1 chromosome with m-BCR rearrangement have been reported (p190 CMPD). We report here 3 new cases of p190 CMPD that had unusual features. In 2 of the cases the m-BCR rearrangement appeared to be a secondary event.

Design and Methods. Patients were studied by cytogenetic, FISH, and molecular biology analyses and followed-up clinically.

Results. The first patient initially had typical 5q-syn-drome, without m-BCR rearrangement. Five years later, she developed hematologic features of CMML, with t(9;22) translocation, m-BCR rearrangement and high levels of p190 BCR-ABL transcript. The second patient initially had hematologic characteristics of chronic myeloid leukemia (CML) with t(9;22) translocation and m-BCR rearrangement but also other complex cytogenetic findings including 17p rearrangement. Monocytosis developed during the course of the disease. The third patient initially had agnogenic myeloid metaplasia (AMM). Five years later, while the hematologic characteristics were still those of AMM, a first karyotype showed a t(9;22) translocation and molecular analysis showed a very low level of p190 BCR-ABL transcript. Four years later, the patient developed hematologic features of atypical CML with blood monocytosis, t(9;22) and much greater (100 fold) p190 BCR-ABL transcript levels.

Interpretation and Conclusions. Our 3 cases and review of the previously published cases show the variability of clinical features of p190 positive CMPD. Our results also suggest that, at least in some cases, p190 BCR-ABL rearrangement could be a secondary event in the course of a myeloid disorder.

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Key words: p190 BCR-ABL, chronic myeloproliferative disease (CMPD), Philadelphia chromosome, myelodysplastic syndrome, monocytosis

The Philadelphia (Ph) chromosome, resulting from the reciprocal t(9;22)(q34;q11) translocation, which carries the hybrid BCR-ABL gene, is found in approximately 90% of patients with chronic myeloid leukemia (CML), and in 2-10% of children and 20-55% of adults with acute lymphoblastic leukemia (ALL).^{1,2} In Ph-positive CML, the breakpoint on the BCR gene nearly always occurs within the major breakpoint cluster region (M-BCR), and the BCR-ABL fusion gene codes for a protein of 210 kDa molecular weight (p210). In most Ph-positive ALL, by contrast, the breakpoint on chromosome 22 occurs within the first intron of the BCR gene, or minor bcr (m-BCR). In these cases, the first BCR exon is fused to ABL exon 2 (e1a2) junction and a BCR-ABL protein of 190 kDa is formed (p190).³

There were been very few reports of Ph-positive CML cases with breakpoints outside the M-BCR, i.e. just upstream (5') or downstream (3') of the M-BCR,^{4,5} whether accompanied or not by interstitial deletions in the M-BCR region.^{6,7}

Eleven cases of Ph positive chronic myeloproliferative disorders (CMPD) with a chromosome 22 breakpoint in the m-BCR, resulting in P190 type BCR-ABL (8 to 18) have been reported, to our knowledge. We describe here 3 new cases, 2 of which were atypical because the m-BCR rearrangement seemed to be a secondary event.

Design and Methods

Case #1

A 58-year old woman (patient #1, Table 1) with a 5-year history of refractory anemia was admitted to Hospital in September 1996. She had no organomegaly. Her hemoglobin (Hb) level was 6.5 g/dL, platelet count $26 \times 10^9/L$ and white blood cell (WBC) count $22 \times 10^9/L$ with 52% neutrophils, 4% eosino-

Correspondence: C. Preudhomme, M.D., Laboratoire d'Hématologie A, Hôpital Calmette, 59045 Lille, France.
Phone: international +33-3-20445880 - Fax: international +33-3-20445510 - E-mail: cpreudhomme@chru-lille.fr

phils, 37% monocytes, 2% immature granulocytes and 4% blasts cells. The bone marrow aspirate was hypercellular with granulocytic hyperplasia, 11% blast cells and 4% erythroblasts. Important dysplastic features were observed: hypogranulation and pseudo Pelger-Huët hypolobulation of neutrophils and hypolobulation of megakaryocytes but only mild dyserythropoiesis. The bone marrow karyotype revealed 2 clones: 44, XX, del(5) (q13q33), add(13)(p11), -17, -18, add(20) (q12), -21, +mar1(4)/ 44-45, idem, (0-1) inv(1) (p11q25), t(9;22)(q34;q11), +(0-1)der(22) t(9;22) (q34;q11).¹⁰

Fluorescence *in situ* hybridization (FISH) was performed on metaphase spreads obtained in September 1996. The BCR-ABL probe (Vysis, Woodcreek, IL, USA), confirmed the BCR-ABL fusion with a split of the BCR gene in the first intron (Figure 1A) and the CSF1 receptor probe confirmed the 5q deletion on the same sample (Figure 1B).

Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of BCR-ABL showed a P190 transcript. On 2% agarose gel staining with ethidium bromide, the intensity of the specific band was similar to that observed after RT-PCR analysis of RNA from the TOM1 cell line, which has a m-BCR rearrangement.

Retrospective blood and bone marrow analyses confirmed the diagnosis of refractory anemia in May 1995 samples. At that time, the patient's Hb level was 11 g/dL with a normal MCV, WBC count $5.6 \times 10^9/L$, with 69% neutrophils, 6% monocytes, and platelet count $330 \times 10^9/L$. The bone marrow was normocellular with fewer than 5% blasts. Minor dyserythropoiesis was seen but the majority of megakaryocytes were unilobulated. At that time, karyotyping was not performed. FISH using the CSF1 receptor probe (5q31) (Vysis) and a D5S23 probe (5p13) (Vysis) demonstrated the 5q deletion on interphase cells obtained in May 1995. However, FISH showed no BCR-ABL fusion in the same May 1995 samples (data not shown). Finally, a mutation in exon 7 of the p53 gene was detected by single strand conformation polymorphism (SSCP) analysis in September 1996 samples (no p53 study was performed on the May 1995 samples). In October 1996 the patient's WBC count rose to $141 \times 10^9/L$ with $24 \times 10^9/L$ monocytes, 15% immature granulocytes and 9% blast cells. She died one month later.

Case #2

A 49-year old man (patient #2, Table 1) presented in November 1997 with hyperleukocytosis. He had a palpable spleen and liver, but no palpable lymph nodes. His Hb level was 9.5 g/dL, platelet count $542 \times 10^9/L$ and WBC count $224 \times 10^9/L$ with 35% neutrophils, 1% eosinophils, 0% basophils, 3% lymphocytes, 1% monocytes, 35% immature granulocytes, 1% nuclear red blood cells and 25% blast cells. The bone marrow aspirate was hypercellular with 55% granulocytic cells, 18% blast cells and 18% erythroblasts. No dysplastic features of the granulocytic and erythro-

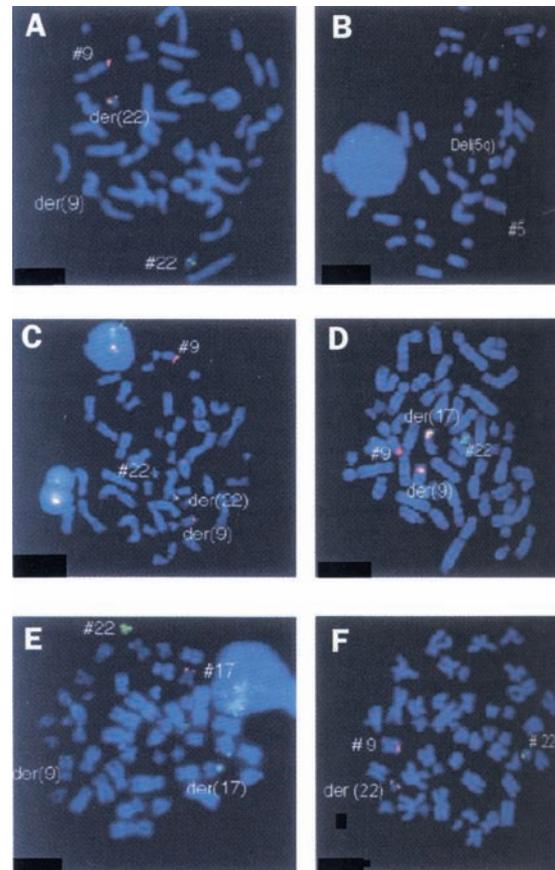


Figure 1.

A) FISH analysis on metaphase of patient #1 with BCR probe (green) and ABL probe (red) showing a BCR-ABL fusion on the der(22) chromosome and a BCR signal on the der(9) chromosome confirming a rearrangement in the minor locus of the BCR gene.

B) FISH analysis on metaphase of patient #1 with CSF1 probe (red) located in 5q31 and D5S23 (green) located in 5p13, showing a deletion on the CSF1 probe on the del 5q chromosome.

C) FISH analysis on metaphase of patient #2 with the Vysis ES BCR-ABL probe (BCR was labeled with spectrum green (green) and ABL was labeled with spectrum orange (red) showing a BCR-ABL fusion on the der (22) chromosome and an ABL-BCR fusion on the der(9) chromosome confirming a rearrangement in the minor locus of the BCR gene.

D) FISH analysis on metaphase of patient #2 with the Vysis ES BCR-ABL probe (BCR was labeled with spectrum green (green) and ABL was labeled with spectrum orange (red) showing amplification of the BCR-ABL fusion gene on the der(17) chromosome and an ABL-BCR fusion on the der(9) chromosome.

E) Whole chromosome painting with spectrum green labeled probe for chromosome 22 (green) and spectrum orange labeled probe for p53 (red) located in 17p13.1 showing a normal chromosome 22, part of chromosome 22 on der(9) and der(17) chromosome and only one p53 signal on a normal chromosome 17 for patient #2.

F) FISH analysis on metaphase of patient #2 with the Vysis ES BCR-ABL probe (BCR was labeled with spectrum green (green) and ABL was labeled with spectrum orange (red) showing a BCR-ABL fusion on the der(22) chromosome, a BCR on normal chromosome 22, and an ABL-BCR fusion on normal chromosome 9. No ABL-BCR signal was observed.

blastic series were observed, but the number of megakaryocytes, which were small and clustered, had increased. The bone marrow karyotype showed 4 clones: 46, XY(1)/46, XY, inv(3)(q22q26), t(9;22)(q34;q11)(4)/45, idem, -7(7)/45, XY, inv(3)(q21q26), der(9) t(9;22)(q34;q11), -17, -22, dic(22;17)(22pter→22q11: :17p12→17qter).⁴

A diagnosis of CML was made.

FISH analysis with a Vysis ES BCR-ABL probe showed one fusion signal (ABL-BCR) on the derivative chromosome 9 and the other fusion signal (BCR-ABL) on the free derivative chromosome 22 (Figure 1C) or on the translocated derivative chromosome 22 (Figure 1D). Translocation of the Ph chromosome on the 17p arm was confirmed using whole chromosome painting of chromosome 22. This translocation induced both the deletion of one p53 allele, as shown by the p53 cosmid probe (Figure 1E), and the tandem duplication of the bcr-abl at the chromosome junction.

Molecular analysis showed strong expression of the p190 BCR-ABL transcript (e1a2). On 2% agarose gel staining with ethidium bromide, the intensity of the specific band was similar to that observed after RT-PCR analysis of RNA from the TOM1 cell line. The patient received hydroxyurea, which normalized the WBC count. Two months later, the WBC count increased to $110 \times 10^9/L$ with $17 \times 10^9/L$ neutrophils, $3.3 \times 10^9/L$ eosinophils, $4.4 \times 10^9/L$ basophils, $6.6 \times 10^9/L$ lymphocytes, $34 \times 10^9/L$ monocytes, 12% immatures granulo-

cytes and 28% blasts. Pseudo Pelger-Huët hypolobulation of the neutrophils and basophils was seen. At that time, immunochemistry using a p53 antibody D07 (Dakopatts, Globstrup, Denmark), showed expression of the p53 protein in 23% of the bone marrow cells and point mutation in exon 8 of the p53 gene was detected by SSCP. The patient died 1 month later.

Case #3

A 61-year old woman (patient #3, Table 1) was admitted to the hospital in 1988 because of anemia and leukopenia. She had a palpable spleen, but liver and lymph nodes were not palpable. Her Hb level was 10.3 g/dL, platelet count $327 \times 10^9/L$ and WBC count $3.7 \times 10^9/L$ with 60% neutrophils, 0% eosinophils, 2% basophils, 17% lymphocytes, 8% monocytes, 7% immatures granulocytes, 4% nuclear red cells, 2% blast cells and many teardrop erythrocytes. The bone marrow aspirate was hypocellular with few megakaryocytes, 35% granulocytes including 29% neutrophils and 55% erythroblasts. The marrow biopsy was normocellular with collagen fibrosis and an increase in reticulin fibers. A diagnosis of agnogenic myeloid metaplasia (AMM) was made. The patient received no treatment. In 1993, blood karyotyping showed 46XX(2)/46XX, t(9;22)(q34;q11).⁴ However, e1a2, e1a3, b2a2, b3a2, b2a3 or b3a3 BCR-ABL transcript by RT-PCR or Southern blot rearrangement using the transprobe 1 (Oncogene Science, Paris, France) was

Table 1. Clinical, hematologic features and outcome of published cases of p190 CMPD.

N°	Age (yrs)	Sex	Leuko-cytes ($\times 10^9/L$)	Imm-granul. (%)	Baso-philis (%)	Monocytes ($\times 10^9/L$) (%)	Myelodyspl. features	Palpable Spleen	Palpable Liver	Cytogenetic rearrangements	Disease stage	Acute leukemia	Survival (months) in addition to Ph1	Ref.
1	57	F	22	2	<1	37 8.1	Yes	+	-	del 5q,-17,-18,-21 and others	ACC	No	died 2	Case #1 present report
2	49	M	224* (110)	35* (12)	<1* (4)	1* 2.2* (30) (34)	Yes	+	+	inv (3),-7,-17	ACC	No	died 3	Case #2 present report
3	61	F	3.7* (19.5)	7* (20)	2* (11)	8* 0.5* (10) (1.9)	No	+	-	None	CP	No	alive 120+	Case #3 present report
4	44	F	56.8	19	2	12 6.8	NR	-	-	None	CP	No	alive 60+	9
5	77	F	63.3	38	1	4 2.5	NR	-	-	None	CP	No (ACC after 18 mos)	NR	10
6	65	M	174	27	4	22 38	NR	+	+	None	ACC	ND	NR	12
7	83	F	32.5* (91.2)	15* (16)	0* (3)	20* 6.5* (23) (20.9)	Yes	+	-	-Y	CP	No	died 20	13
8	62	M	79.6	NR	NR	NR NR	NR	+	+	-Y	CP	Yes	died 36	14
9	47	M	225	40	<1	2 4.5	NR	+	-	None	CP	No	died	15
10	52	M	180	24	13	6 10.8	NR	+	NR	None	CP	No	alive 23+	16
11	75	M	227	25	<1	21 47.7	No	+	-	None	CP	No	alive 3+	17
12	49	M	73.9	25	1	32 23.6	Yes	-	-	None	CP	Yes	alive 18+	19

NR: not reported, CP: chronic phase; ACC: accelerated phase; *(-) numbers in parentheses are the values at the last examination.

not observed. FISH, performed on interphase cells using a M-BCR probe (Appligene Oncor, Illkirch, France) revealed no BCR-ABL fusion, but deletion of one BCR gene (data not shown). In November 1997, the Hb level was 9.8 g/dL, platelet count $192 \times 10^9/L$, and WBC count $19.5 \times 10^9/L$ with $7.8 \times 10^9/L$ neutrophils, $0.2 \times 10^9/L$ eosinophils, $2.1 \times 10^9/L$ basophils, $2.1 \times 10^9/L$ lymphocytes, $1.95 \times 10^9/L$ monocytes, $3.9 \times 10^9/L$ immature granulocytes, $0.78 \times 10^9/L$ nuclear red blood cells and $1.35 \times 10^9/L$ blasts. Karyotyping, performed on blood cells, showed 46XX (1)/46XX, t(9;22)(q34;q11)(19). A new molecular analysis still showed a p190 (e1a2) BCR-ABL transcript. The signal observed in the patient was comparable to the signal observed with a 10^{-2} dilution of the TOM1 positive cell line.

Retrospective study of the sample obtained in 1993 confirmed the presence of the p190 (e1a2) transcript at a level comparable to that of a 10^{-4} dilution of TOM1 cell line after nested PCR. Neither PCR primers used for the detection of p210 BCR-ABL, nor specific primers for other transcripts including p230 BCR-ABL⁸ allowed detection of transcripts others than p190 BCR-ABL. FISH analysis, performed on metaphases obtained in May 1998 using a BCR-ABL ES probe (Vysis), confirmed the BCR-ABL fusion on the derivative chromosome 22 and the ABL-BCR deletion on the derivative chromosome 9 (Figure 1F).

Discussion

Ph1 positive chronic myeloproliferative disorder (CMPD) with a breakpoint in the minor locus of the BCR gene (p190 CMPD), appears to be a very rare disease. In addition to the three present cases, only eleven other cases have been reported in the literature, to our knowledge, 9 of them in detail.^{9,10,12-17,19} The median age was 61 years (range 44 to 83) and the M/F ratio was 1.5 (Table 1). A palpable spleen was present in 6 cases. The WBC count increased in 9 patients, and was greater than $50 \times 10^9/L$ in 8 cases. Circulating immature granulocytes were found in all cases; the percentage of these granulocytes was greater than 15% in 7 cases. One case (#6 in Table 1) was in accelerated phase disease with an increasing percentage of marrow blasts, and 7% of circulating blasts. Circulating monocytosis above $1 \times 10^9/L$ was seen at diagnosis or during disease evolution in all cases but one, however the percentage of monocytes in the differential count was greater than 10% in only 5 cases. Basophilia above 3% was seen in 3 patients with a median follow up of 20 months (range 2 to 120). Only 2 of the 9 patients had progressed to AML (one after 18 and one after 36 months). A classification of the 9 previously published cases (#4 to #12 in Table 1) on the basis of hematologic features (absolute count and percentage of circulating monocytes, percentage of immature granulocytes and basophils),²⁰ before the results of cytogenetics and BCR-ABL analysis, was difficult in several cases (Table 1). Two patients (#5 and

#9) had relatively typical features of classical CML including high WBC count, low monocyte percentage, high percentage of immature granulocytes but neither of them had basophilia. One case (#7) had relatively typical features of CMML (moderate hyperleukocytosis, monocytes >10% and immature granulocytes <15%), but a high WBC count ($91 \times 10^9/L$) and basophilia, which are unusual in CMML, were subsequently seen. Four other patients (#6, #9, #11 and #12) had atypical features and it was hard to classify them into having either CML, atypical CML²¹ or CMML. Indeed they had prominent monocytosis (>10%), but also >15% immature granulocytes, and 3 of them had a WBC count $>100 \times 10^9/L$ and 2 had basophilia, which are unusual features in CMML. Finally, patient #10 had hematologic features relatively typical of CML, but with 6% monocytes (ie $10.8 \times 10^9/L$). In all but two cases, which showed loss of chromosome Y, Ph chromosome was the only cytogenetic abnormality.

The three cases reported here (#1-3, Table 1) all seemed to differ somewhat from the previously published cases of p190 CMPD. Our case #2 presented with characteristic hematologic features of CML, except for the absence of basophilia, but had complex additional cytogenetic abnormalities including inv(3), -7, and -17. Our case #1 presented with MDS, with typical features of the 5q- syndrome. Presence of 5q deletion and absence of BCR-ABL rearrangement at that stage could be retrospectively confirmed by FISH. The patient progressed to having a typical hematologic picture of CMML. This case therefore appears to be the second reported case of Ph1 positive CMPD with an m-BCR rearrangement and typical features of CMML, (i.e. moderate hyperleukocytosis, high monocyte percentage, low percentage of immature granulocytes and basophils in peripheral blood), a disorder in which del 5q is a very rare cytogenetic finding. A small number of cases of MDS other than CMML with m-BCR rearrangement have been reported,²² but none of the previously reported cases of p190 CMPD has a detectable phase with MDS features. In our case #1, molecular and cytogenetic studies showed that the occurrence of t(9;22) translocation and m-BCR rearrangement was clearly a secondary event accompanying or perhaps inducing transformation to a hematologic pattern of CMML.

Our case #3 presented with hematologic features of AMM, which have not been previously reported in p190 CMPD, to our knowledge. Monocytosis and basophilia appeared during the course of the disease. At diagnosis this patient had a low level of p190 BCR-ABL transcripts, without others BCR-ABL transcripts (p210 or p230). The level of the p190 BCR-ABL transcripts increased between 1993 to 1998 (10^{-4} to 10^{-2}). This was associated with clinical evolution, raising the possibility that the m-BCR rearrangement was acquired during the progression of the disease.

In the previously reported cases of p190 CMPD, Ph1 was the only cytogenetic alteration except in two cas-

es, in which the Y chromosome had also been lost. By contrast, 2 of our 3 cases had complex additional cytogenetic rearrangements including chromosome 17 alteration leading to 17p deletion and therefore loss of one p53 allele, whereas the other p53 allele was mutated. Pseudo-Pelger-Huët hypolobulation of granulocytes, correlated strongly in our experience to 17p deletion, was also present in both cases.²³ The presence of pseudo-Pelger hypolobulation was not reported in the previously published cases of p190 CMPD, nor was p53 status evaluated in these patients. 17p deletion, p53 mutation and pseudo-Pelger hypolobulation are also features of CML that are acquired during accelerated or acute phases of disease.²⁴ Our 2 patients with 17p deletion had indeed a particularly short survival (2 and 3 months). No 17p deletion was cytogenetically present in our third case, which had neither p53 mutation nor pseudo-Pelger hypolobulation and is still alive more than 10 years after diagnosis.

Most of the reported cases of p190 CMPD showed, at some point, blood monocytosis. A relationship between p190 BCR-ABL and monocytic lineage proliferation was also reported in Ph⁺ AML (M4 or M5a) with a m-BCR breakpoint²⁵ but, on the other hand, we did not find any m-BCR rearrangement in a relatively large series of patients with typical CMML.²⁶

In conclusion, our findings highlight the variety of hematologic features of p190 CMPD and suggest that, at least in some cases, m-BCR rearrangement could occur as a secondary event in a chronic myeloid disorder. We suggest that m-BCR rearrangements should be analyzed in all cases of atypical MPD, especially when blood monocytosis develops during the course of the disease.

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