short report
Haematologica 1997; 82:336-337

DUPLICATION OF THE DER(13)t(12;13)(p13;q14) IN CHRONIC MYELOMONOCYTIC LEUKEMIA

GIUSEPPINA FUGAZZA, RAFFAELLA CERRI*, ROBERTO BRUZZONE, FRANCO PATRONE, MARIO SESSAREGO
*Department of Internal Medicine (DIMI), University of Genoa and *First Division of Hematology, S. Martino Hospital, Genoa, Italy*

ABSTRACT

A case of chronic myelomonocytic leukemia with a reciprocal translocation (12;13)(p13;q14) and other numerical and structural abnormalities is described. Most of the metaphases examined showed duplication of the der(13)t(12;13), leading to trisomy of the translocated segment of chromosome 12. Using fluorescence *in situ* hybridization we observed that the breakpoint on chromosome 13 is centromeric to the retinoblastoma gene.

Since other cases with apparently similar t(12;13) have recently been reported, we conclude that this structural rearrangement may be a rare but non random event in hematologic disorders.

Key words: chronic myelomonocytic leukemia , translocation (12;13), FISH

Deletions as well as translocations of the terminal band of the short arm of a chromosome 12 are a recurring abnormality that can be found in hematological diseases.[1]

The t(5;12)(q33;p13) is frequently described in chronic myelomonocytic leukemia (CMMoL), often with eosinophilia,[2,3] but other hematological disorders involving the 12p13 band and several other chromosomal bands as partners have been reported: 3q26;[4] 7q11;[5] 8p22;[5] 9q34;[6] 10q24;[3] 12q13;[7] 13q14;[5,8,9] 17q21;[10] 21q22;[11] 22q12.[12]

We report a case of CMMoL with a complex karyotype characterized by the presence of a t(12;13)(p13;q14) and by duplication of the der(13). Fluorescence *in situ* hybridization (FISH) confirmed the reciprocity of the translocation and the relocation of the retinoblastoma gene (RB1) to the der(12).

Case Report

A 70-year-old woman was admitted to the gynecology department for lower abdominal pain related to polycystic ovarian disease in November 1995. A complete blood count revealed: hemoglobin (Hb) 10.3 g/dL; white blood cell (WBC) count 18.5×10^9/L, with neutrophils 68%, eosinophils 1%, lymphocytes 16%, monocytes 14%, myelocytes 1%; platelets 60×10^9/L. Lactate dehydrogenase was 1,850 U/L (normal values 230-460 U/L). Serum creatinine was 2.7 mg/dL (normal values 0.5-1.3 mg/dL). The patient had suffered from moderate hypertension for years. One month later congestive heart failure appeared; serum creatinine had risen to 3.2 mg/dL. She was admitted to our department in March 1996 for persistent fever. Hb was 9.8 g/dL, the WBC count 24×10^9/L with mature monocytosis and some blast cells; platelets 46×10^9/L. Bone marrow (BM) examination showed myeloid hyperplasia with 7% myeloperoxidase-positive blast cells, an increase in monocytes and a decrease of megakaryocytes. Erythropoiesis appeared to be reduced and there were dyserythropoietic features. A portion of the BM sample was used for cytogenetic analysis. Further clinical and laboratory investigations confirmed the diagnosis of CMMoL, heart failure and chronic kidney failure. The patient was treated with hydroxyurea for the hematologic disease, without benefit. The WBC count in May 1996 was 32×10^9/L, with neutrophils 51%, eosinophils 1%, lymphocytes 22%, monocytes 15%, myelocytes 6% and blasts 5%.

She died of infection-related complications and heart failure.

Materials and Methods

Cytogenetic analysis. Chromosome analysis was performed on BM cells routinely processed after 24 h of culture. Cells fixed in 1:3 glacial acetic acid: methanol were utilized for both Q-banding and FISH techniques.

FISH. We used the following biotinylated probes: the retinoblastoma DNA probe mapping on the 13q14.2 band (Oncor, Gaithersburg, MD, USA) and the chromosome 12 painting probe (Bouty, Milan, Italy). Before hybridization, slides were treated with RNase and proteinase K and denaturation, hybridization and posthybridization washings used for each probe were as specified by the manufacturer. Detection was performed with avidin-FITC (Vector Laboratories). Propidium iodide or DAPI was used as counterstain.

Correspondence: Dr. Mario Sessarego, Department of Internal Medicine, University of Genoa, viale Benedetto XV 6, 16132 Genova, Italy.
Ackowledgements: This research was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC - Milano) and by CNR grants n. 95.02441.CT04 and PF-ACRO n. 95.00409.39. The authors thank Sara Beltramea for her excellent assistance in the preparation of the manuscript.
Received December 30, 1996; accepted March 13, 1997.

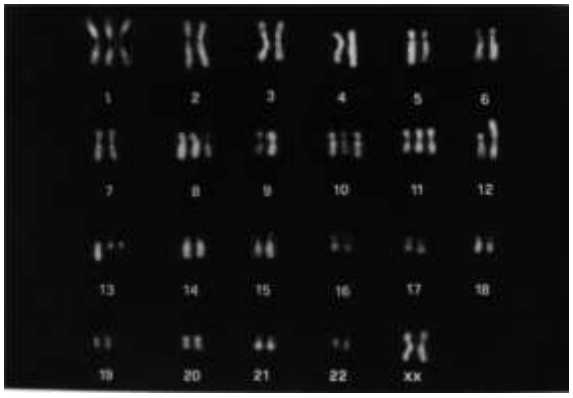

Figure 1. Q-banded karyotype: 51,XX,+i(1q),+8,+10,+11, t(12;13)(p13;q14), +der(13)t(12;13).

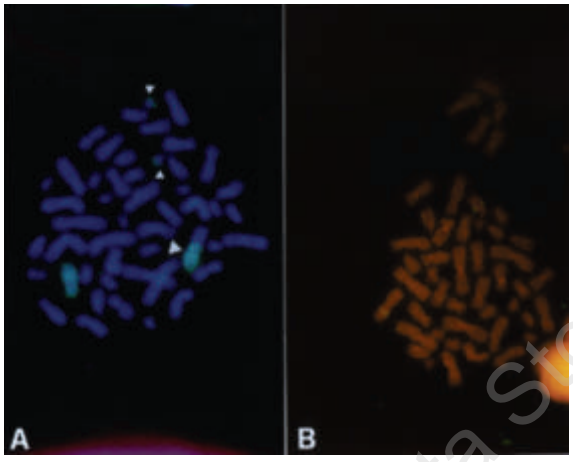

Figure 2. Two bone marrow metaphases examined by FISH analysis using: A. a painting 12 probe showing the 12p+ (large arrowhead) and the two der(13)t(12;13) (small arrowheads); B. the RB1 gene. The arrowhead indicates the der(12)t(12;13) with the RB1 signal.

Results and Discussion

The majority of the metaphases examined showed a hyperdiploid karyotype characterized by trisomy 8, 10 and 11, by a supernumerary i(1q) and by the presence of a t(12;13)(p13;q14) with duplication of the der(13) (Figure 1).

Four of the five cases with a t(12;13)(p13;q14) previously reported in the literature had been diagnosed as acute leukemia (2 as acute non lymphoblastic leukemia and 2 as lymphoblastic leukemia) and the fifth as a blastic phase of chronic myeloid leukemia.[5,8,9] The patient reported here showed hematological features compatible with CMMoL in a seemingly non aggressive phase. BM analysis revealed hyperplasia of the myeloid lineage without eosinophilia with differentiation and maturation capacities; monocytosis and dysmyelopoiesis (hypogranulated neutrophils, micromegakaryocytes) were evident but the amount of blast cells was low. Cytogenetic analysis, unlike the hematological features, revealed a complex karyotype indicative of an advanced phase of the disease. The 32 metaphases examined were: 46,XX [3 cells]/50, XX,+i(1q),+8,+10,+11,t(12;13)(p13;q14) [4 cells]/51,XX,+i(1q),+8,+10,+11,t(12;13)(p13;q14), +der(13)t(12;13) [25 cells].

In our case, FISH analysis performed with a painting 12 probe revealed the presence of chromosome 12 sequences on the der(13)t(12;13), confirming the reciprocity of the translocation (Figure 2A). Duplication of the der(13)t(12;13) generated trisomy of the translocated segment of chromosome 12. The RB1 tumor suppressor gene mapping on the 13q14 band is translocated to the der(12) t(12;13) (Figure 2B) as in the two cases studied with the FISH technique,[9] indicating that the breakpoint on chromosome 13 is centromeric to the gene. Further molecular analyses are needed to establish the breakpoints of this particular translocation, which appears to be a rare but not random cytogenetic abnormality observed both in myeloid and lymphoid leukemias.

References

1. Berger R, Bernheim A, Le Coniat M, et al. Abnormalities of the short arm of chromosome 12 in acute nonlymphocytic leukemia and dismyelopoietic syndrome. Cancer Genet Cytogenet 1986; 19:281-9.
2. Berkowicz M, Rosner E, Rechavi G, et al. Atypical chronic myelomonocytic leukemia with eosinophilia and translocation (5;12). A new association? Cancer Genet Cytogenet 1991; 51:277-8.
3. Wlodarska I, Mecucci C, Marynen P, et al. TEL gene is involved in myelodysplastic syndromes with either the typical t(5;12)(q33;p13) translocation or its variant t(10;12)(q24;q13). Blood 1995; 85: 2848-52.
4. Raynaud SD, Baens M, Grosgeorge J, et al. Fluorescence in situ hybridization analysis of t(3;12)(q26;p13): a recurring chromosomal abnormality involving the TEL gene (ETV6) in myelodysplastic syndromes. Blood 1996; 88:682-9.
5. Raimondi SC, Williams DL, Callihan T, Peiper S, Rivera GK, Murphy SB. Nonrandom involvement of the 12p12 breakpoint in chromosome abnormalities of childhood acute lymphoblastic leukemia. Blood 1986; 68:69-75.
6. Okuda K, Golub TR, Gilliland DG, Griffin JD. p210BCR/ABL, p190BCR/ABL, and TEL/ABL activate similar signal transducation pathways in hematopoietic cell lines. Oncogene 1996; 13:1147-52.
7. Heerema NA, Palmer CG, Baehner RL. Karyotypic and clinical findings in a consecutive series of children with acute lymphocytic leukemia. Cancer Genet Cytogenet. 1985; 17:165-79.
8. Zitzelsberger H, Bauchinger M, Wilmanns W, Strauss PG. Cytogenetic and molecular analysis of a "masked" Philadelphia chromosome in chronic and blastic phase of chronic myeloid leukemia. Cancer Genet Cytogenet 1990; 47:219-25.
9. Tosi S, Stilgenbauer S, Giudici G, et al. Reciprocal translocation t(12;13)(p13;q14) in acute nonlymphoblastic leukemia: report and cytogenetic analysis of two cases. Cancer Genet Cytogenet 1994; 77: 106-10.
10. Krance RA, Raimondi SC, Dubowy R, et al. t(12;17)(p13;q21) in early pre-B acute lymphoid leukemia. Leukemia 1992; 6:251-5.
11. Romana SP, Le Coniat M, Berger R. t(12;21): a new recurrent translocation in acute lymphoblastic leukemia. Genes Chromosomes Cancer 1994; 9:186-91.
12. Geurts van Kessel A, Stellink F, van Gaal J, van de Klundert JW, Siepman A, Oosten HR. Translocation (12;22)(p13;q12) as sole karyotypic abnormality in a patient with nonlymphocytic leukemia. Cancer Genet Cytogenet 1994; 72:105.