HAEMATOLOGICA

1990: 75:473-6.

# INV(12) (p13q11) AND DICENTRIC CHROMOSOMES IN A SECONDARY LEUKAEMIA WITH BASOPHILIA *

JEAN-LOUP HURET, ANDRÈ BRIZARD, FRANÇOIS GUILHOT, DOMINIQUE COUET, MICHELE SCHOENWALD, JOHN RK SAVAGE, JOSEPH TANZER

**We report on a case of secondary myelodysplasia with basophilia. A karyotype showed 1) the involvement of 12p, which should be related to the basophilia and/or to previous drug exposure, and 2) the unexpected presence of three different dicentric chromosomes.**

KEY WORDS: Chronic myelomonocytic leukaemia, secondary leukaemia, basophilia, dicentric chromosomes.

Chromosome 12p rearrangements in myeloid malignancies have been reported in chronic myelomonocytic leukaemia [1], in acute non lymphocytic leukaemia (ANLL) type 2 with basophilia[2], and in other myelodysplastic syndromes and ANLL, mostly secondary to carcinogen exposure [4]. We report a case of secondary chronic myelomonocytic leukaemia (CMML) in transformation with basophilia and a 12p rearrangement. This case also exhibited numerous extra copy segments 8q, especially 8q23 → qter, and three various dicentric chromosomes.

## CASE REPORT

A 69-year-old woman was referred to us in February 1986 with hyperthermia and asthenia. She had previously had a malignant melanoma in 1976 treated by surgery and chemotherapy (vinblastine, thiotepa, methotrexate, mitocronomicine and dacarbazine), which was interrupted in 1979. At presentation in 1986, there was no splenomegaly nor enlarged lymphnodes. Haemoglobin was 9.4 g/dl, WBC was $27 \times 10^9$/l with 61% neutrophils, 14% basophils, 8% lymphocytes, 14% monocytes, 2% immature cells and 1% blasts. Platelet count was $52 \times 10^9$/l. Bone marrow smears were hypercellular with 20% blasts, 9% basophils and marked myelodysplastic features affecting all cell lines; a CMML in transformation, according to the FAB classification [5], was diagnosed. The bone marrow karyotype (direct analysis, RHG and C bandings, 50 mitoses analysed) was 46, XX [4 mitoses]/45, XX, **del(5)(q14q34)**, -8, +dic(8)(p11), -6, -12, +dic(6; inv(12)) (p22; (p13q11)) [15 mitoses]/46, XX, del(5q), -8, +dic(8), +dic(8), -6, -12, +dic(6; inv(12)) [29 mitoses]/46, XX, del(5q), -8, +dic(8), -6, -12, +dic(6; inv(12)), +8p+ [2 mitoses]. In the detailed system for chromosome aberrations [6] dic (6; inv(12)) was 6qter → 6p22::12q11 → 12p13::12q11 → 12qter, and 8p+ was 8qter → **8q23::8p22** → 8qter. No improvement was noted with chemotherapy. A frank acute non lymphoblastic transformation occurred five months after diagnosis (WBC was $22 \times 10^9$/l with 30% blasts and 8% basophils). A karyotype from bone marrow (direct analysis, 24-hour and 48-hour culture, RHG and C bandings, 31 mitoses analysed) was 46, XX [1 mitosis]/46, XX, del(5q), dic(6; inv(12)), +dic(8), $8p^+$ [13 mitoses]/46, XX, del(5q), dic(6; inv(12)), +dic(8), $8p^+$, dic (3; 8) (q24; p11) [11 mitoses]/47, XX, del(5q), dic (6; inv(12)), +dic(8), $8p^+$, + DM [4 mitoses]/46, X del(X)(q2?5), del(5q), dic(6; inv(12)), +dic(8), $8p^+$ [2 mitoses] [Fig. 1]. In the detailed system **dic(3;8)(q24;p11)** was 3pter → 3q24::8p11 → 8qter. The patient died in February, 1987 from sepsis and haemorrhagcs secondary to bone marrow insufficiency.

## DISCUSSION

A pericentric inversion of chromosome 12 is a rare anomaly. Only 6 previous cases with well-defined breakpoints have been published, 5 of which occurred in myeloid malignancies [7-10]. The breakpoint in the short arm has been located in p12-p13, whilst the breakpoint in the long arm has been found dispersed in q11, q13, q14, q21 and q23. An inv peri(12)) has been found associated with **del(5q)(3** times), del(6p)(twice), del(13q) or monosomy 13 (twice), and these associations are unlikely to be random.

Basophilia of high degree is quite unusual in haematological malignancies except in chronic myelogenous leukaemia. However, such a basophilia has been described in cases of M2 acute leukaemia with 12p rearrangements [2,3]. More rarely, 12p rearrangements are associated with hypereosinophily [11,12], and the existence of a common basophil-eosinophil progenitor has been ascertained [13]. It is thus possible that a malignant event lying on rearranged chromosome 12p involve a stem cell retaining the potentiality to differenciate along multilineage pathways. Alternatively, chromo-

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*This case was cited in (15).*

*From the Dkpartement d'Hématologie et Oncologie Médicale, CNRS URA 1338, Hôpital Jean Bernard, Poitiers, France, and the MRC Radiology Unit, Chilton, Didcot, Oxon, UK.*

*The authors wish to thank Martine Potiron, Micheline Martin and Marie-Andrée Landreau for technical assistance. This work was supported by Association pour la Recherche sur le Cancer and Ligue Nationale contre le Cancer.*

*Received February 14, 1990; accepted May 16, 1990.*

*Correspondence: Dr. J.L. Huret, Cytogénétique Lab. Hématologie, CHU La Milétrie, F-86021 Poitiers, France.*

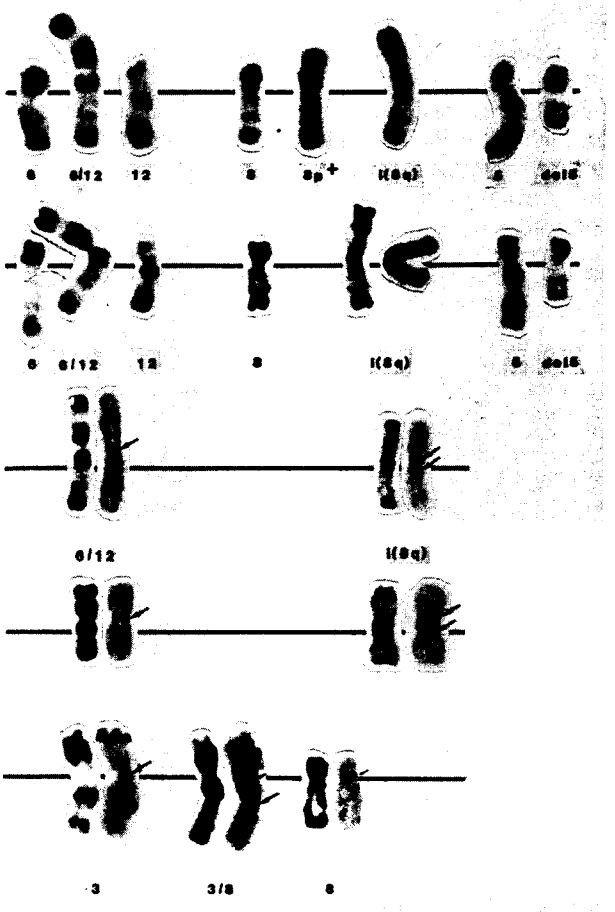


Fig. 1. - Partial karyotypes with RHG banding (above) showing structural anomalies:
dic(6;12): 6qter → 6p22::12q11 → 12p13::12q11 → 12qter
$8p^+$: lqter → 8q23::8p22 → lqter
dic(8)(p11): lqter → 8p11::8p11 → lqter
del(5q)
and below: dic(3;8): 3pter → 3q24::8p11 → lqter.
Below: partial karyotypes with both RHG and C bandings on the same mitoses showing the dicentric chromosomes. Large arrows; detectable centromeres; small arrows: presumed centromeres. The centromere of 12 has moved close to 6p22, confirming the inversion. To be noted that C banding is not present at the centromere of the rearranged chromosome 6.

some 12p rearrangements have also been described in leukaemia following drug exposure for various cancers [4]. It is therefore probable that the presence of a basophilia and the appearance of a secondary leukaemia refer to two usually unrelated events on chromosome 12 short arm. In the present report, 12p rearrangement was found in a secondary leukaemia with basophilia. In certain cases with [illegible] breakpoints, such as in the present report, a drug exposure could be the cause, and the basophilia a consequence of 12p rearrangement.

Recurrent extra copies of 8q, especially 8q23 → qter, were found in each abnormal subclone in the present case. Furthermore, these extra copies were provided by various structural anomalies: dic(8)(p11), and/or $8p^+$, and/or dic(3; 8). Altogether, 8q23 → 8qter was present in 3 to 5 sets in the first sample, progressing to 5 to 6 sets in the second sample. MYC is mapped in 8q24, and MYC gene amplification has been shown to be correlated with tumour progression in various malignancies. However, it is unknown if these extra gene copies were expressed and have therefore played a role in the progression of this secondary myelodysplastic syndrome.

It is striking in this case that each chromosomal anomaly (del(5q), 6p involvement, 12p involvement, ...) seems to add a touch of specificity to the general haematological picture (Table 1). This can be compared to the appearance of a t(15;17) or of a dic(9;12), respectively, in a promyelocytic and a B lymphoblastic transformation of a chronic myelogenous leukaemia with t(9;22) [17, 18].

Table 1. - *Karyotypic anomalies in relarion to the presence of various specificities in this leukaemia.*

| Anomaly | Related specificity | Reference |
|---|---|---|
| del(5q) | → secondary myelodysplasia | (14) |
| 6p involvement | → secondary anomaly (evolution of the disease | (15) |
| | and/or → secondary leukaemia | (16) |
| 12p involvement | → chronic myelomonocytic leukaemia | (1) |
| | and → acute leukaemia with basophilia | (2) |
| | and → secondary leukaemia | (4) |
| 8q23-24 extra copies | —? → progression of the disease | |

An unexpected feature was that three different dicentric chromosomes were found in the present case: dic(6;inv(12)), dic(8), and dic(3;8). This could be related to previous chemotherapy treatment. A mitosis with C-banding (Fig. 2) was shown to exhibit a rearranged dicentric chromosome (i.e. with change in chromosome length and centromeric indexes). Unfortunately, this mitosis was not R or G banded previously to C-banding, and the ex-

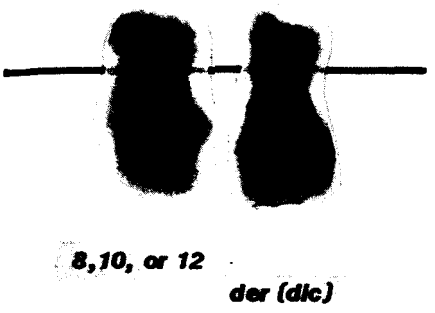


Fig. 2. - Rearranged dicentric chromosome with C-banding (right) and a chromosome C (8,10 or 12)(left), included for comparison of the length of the dic.

act nature of the rearrangement is unknown. However, this finding could be in favour of the existence of a true dicentric surviving through a breakage-fusion-bridge cycle. By another way (i.e. a double bridge at anaphase), true dicentric chromosomes have already been ascertained to occur in malignancy [19]. It is impossible to say if all the centromeres of the dicentric chromosomes were active in our case. In the case of true dicentric chromosomes, especially those with a large intercentromeric region such as dic(3;8), the cells bearing these chromosomes should be highly unstable and selected against, but the cell lines appeared to be well established. The main hypothesis would be that these particular dicentrics gave specific selective advantages to the cells carrying them to counterbalance a gross mechanic disadvantage. These specific advantages could be those involved in the malignant process and discussed above. The alternative hypothesis could be that an unknown disregulation favoured the repeated «fall free» of dicentric chromosomes to maintain their presence in the abnormal clones.

## INV(12) (p13q11) E CROMOSOMI DICENTRICI IN UN CASO DI LEUCEMIA SECONDARIA CON BASOFILIA

**Viene descritto un caso di leucemia secondaria con basofilia. L'esame citogenetico ha dimostrato il coinvolgimento di 12p (potenzialmente importante per la basofilia) e 3 diversi cromosomi dicentrici.**

*Note added after submission:* A very comprehensive study on true and pseudo dicentrics has recently been published (Vig et al, Cancer Genet Cytogenet **1989; 43: 151).**

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