*short report*

*Haematologica 1994; 79:83-5*

# TRISOMY 4 AND RING CHROMOSOME IN A PATIENT WITH ACUTE MYELOMONOCYTIC LEUKEMIA

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**ABSTRACT**

**We describe a patient with acute myelomonocytic leukemia (AMML) in whom cytogenetic analysis revealed trisomy 4 associated with a ring chromosome. In addition, in a cytogenetically unrelated clone, trisomy 8 and 5q– abnormalities were detectable. The possibility of a subclinical myelodysplastic syndrome preceding the onset of AML is discussed on the basis of the morphological and cytogenetic findings.**

*Key words: trisomy 4, acute myelomonocytic leukemia, ring chromosome*



Trisomy 4 is a rare cytogenetic abnormality proposed as an acute myeloid leukemia (AML)-specific aberration.[1] It is particularly associated with the M4 FAB subtype and occurs in well below 1 percent of all AML cases. Occasionally, trisomy 4 has been observed in acute lymphoblastic leukemia.[2]

Here we describe a patient suffering from acute myelomonocytic leukemia (AMML), in whom cytogenetic analysis revealed trisomy 4 in association with a ring chromosome. In addition, in a cytogenetically unrelated clone trisomy 8 and 5q– were detected. Finally, myelodysplastic abnormalities involving all hemopoietic lineages were observed at morphologic examination.

### *Case report*

A 70-year-old male was admitted to our institution for persistent fever and weakness. The patient's previous history showed no severe illness or any exposure to mutagens. On admission, anemia (Hb 8.3 gr/dL) and thrombocytopenia (platelets: $23\times10^9$/L) were found. White blood cell count and differential showed: WBC $11\times10^9$/L, with 58% myelomonocytoid blasts, 14% neutrophils, 18% lymphocytes, 10% monocytes. Bone marrow examination showed 55% infiltration of myelomonocytoid blasts; the remaining cell population consisted of partially maturing cells characterized by grossly dysplastic trilineage changes.

Cytochemical staining showed clear positivity for myeloperoxidases and $\alpha$-naphthylacetate-esterase in 20% and 15% of blast cells, respectively.

Immunophenotypic study performed on both bone marrow and peripheral blood, as previously described[3] demonstrated clear positivity for CD34, CD13, CD14 and DR antigens. A diagnosis of AMML was formulated.

The patient was unsuccessfully treated with an induction therapy consisting of a combination of idarubicin/ARA-C,[4] and died from severe sepsis in the setting of progressive disease following a prolonged hypoplastic phase.

### *Cytogenetic analysis*

Chromosome analysis of bone marrow was performed by standard methods; RHG banding was employed and chromosomes were classified according to the International System of Human

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*Received on October 1, 1993; accepted on December 16, 1993.*

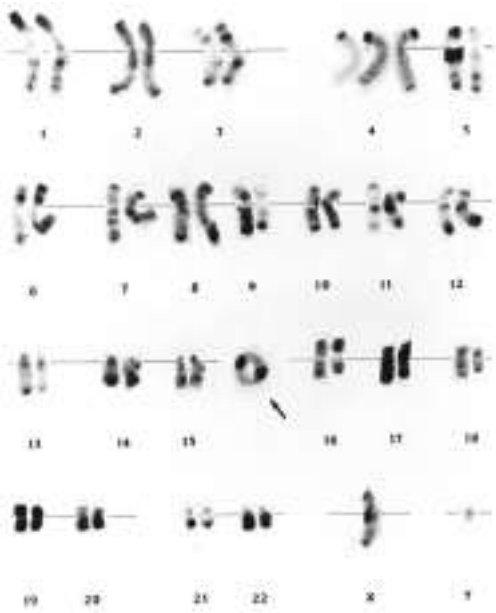

Figure 1. 48, XY, +4, +r(3) (p24q27); r(3); extra chromosome is indicated by the arrow.

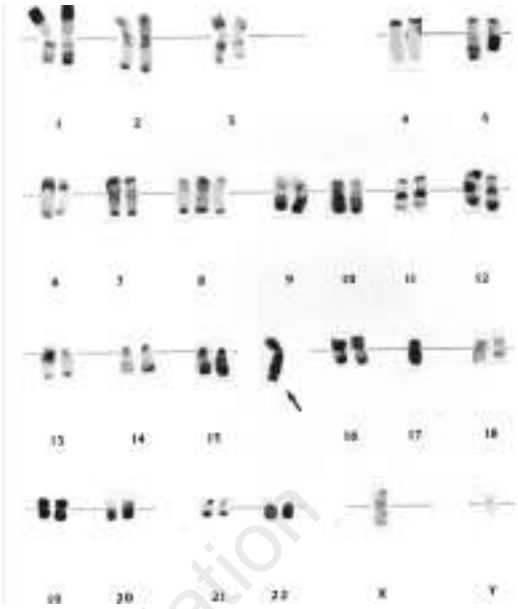

Figure 2. 47, XY, +8, +del(5)(q13q31), –17, +der(9)t (9;17)(q22q12); der(9)t(9;17); extra chromosome is indicated by the arrow.



Cytogenetic Nomenclature (ISHCN).[5]

Sixty metaphases were observed. The patient's karyotype is illustrated in Table 1 and Figures 1 and 2.

### *Discussion*

As an isolated cytogenetic abnormality, trisomy 4 has been associated with a particular subset of AML characterized by dysplastic features of all bone marrow lineages, suggesting involvement of an early myeloid hemopoietic stem cell.[1]

In our patient, the presence of an independent clone lacking the extra chromosome 4 and characterized by trisomy 8 and 5q– abnormalities, both commonly found in myelodysplastic syndromes (MDS), strongly supports the hypothesis that a subclinical MDS preceded the onset of apparently *de novo* AML. Trilinear dysplastic changes in the bone marrow, as well as poor response to chemotherapy add further weight to this possibility.

In a recent review of trisomy 4 in AML, Pedersen reported a median survival of 17 months; the percentage of trisomic metaphases was an independent adverse prognostic factor, suggesting that this chromosomal abnormality is associated with poor prognosis in AML patients.[6] More recently still, Zollino et al. described an AML patient in whom blast cell trisomy 4 was associated with 5q–.[2]

The situation was more complex in our patient because of the presence of two cytogenetically unrelated clones, possibly indicating hematopoietic biclonality. Multiple chromoso-

Table 1. Patient karyotype.

| | | |
|---|---|---|
| 46 XY | 36/60 | 60% |
| 48, XY, +4, +r(3) (p24q27); r(3) | 15/60 | 25% |
| 47, XY, +8, +del(5)(q13q31), -17,+ der(9)t(9;17)(q22q12) | 9/60 | 15% |

mally unrelated cell populations have been detected in MDS: either emerging during the course of the disease, or disappearing or becoming undetectable during subsequent clinical evolution. In particular, the former of these possibilities has consistently been associated with progression to more malignant conditions such as AML.[7]

We feel that the emergence of trisomy 4 represented a major event in determining the transformation from MDS to AML, as has recently been reported for evolution from benign sex cord/stromal tumor to ovarian thecoma.[8] Whether trisomy 4 can influence the proliferation and self-perpetuation of malignant cells remains unclear at present. Some genes involved in the mechanisms of cell growth control have been mapped on chromosome 4,[9] so one may speculate about a gene-dosage effect in determining the progression of malignancy in our patient. However, simple overexpression cannot be considered an absolute indication that an oncogene is directly involved in the regulation of cell proliferation, as was demonstrated for the c-kit oncogene in a case of AML with trisomy 4.[10]

Finally, the exact significance of a ring chromosome, frequently found in solid tumors but extremely rare in hematologic malignancies, requires further investigation.



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