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DUPLICATION OF THE LONG ARM OF CHROMOSOME 1, IN PRIMARY MYELOFIBROSIS IS A MALIGNITY FACTOR?

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Introduction

The Myeloproliferative Neoplasms (MPN) is a heterogeneous group of Myeloid Neoplasms (MN) that are characterized by an excessive proliferation of one or more lineages of the myeloid series.[1]

Primary myelofibrosis (PMF) is one of the MPN which presents a preferential proliferation of megakaryocytes and granulocytes in the bone marrow (BM).

One of the causes of morbidity and mortality in PMF is the progression to Acute Myeloid Leukemia (AML).

Most frequent cytogenetics anomalies observed in PMF are del(20q) and partial trisomy 1q; gains of chromosomes 9 and/or 8 have also been reported.[2]

Methods

Patient Report

The patient characterization is summarized in Table 1.

Cytogenetics, Fish, and Microarray analyses

Chromosome analysis has done, from cultured cells of bone marrow, without stimulation.

FISH analysis on metaphase plates of the patient was carried out using the library probe for chromosome 1 (wcp1)[8].

Microarray analyses of the patient DNA was processed according to the Affymetrix manual protocol Affymetrix® Cytogenetics Copy Number Assay P/N 703038 Rev.3.

Molecular Analysis

The screening of the mutation V617F in the gene JAK2 was done as described Baxter *et al* (2005).[9]

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Table 1: Clinical presentation Cytogenetics, FISH analyses and *JAK2* mutation result of the patient studied.

Diagnosis	Sex	Age	Biochemical diagnosis	Observation	Karyotype	FISH Analyses	*JAK2* V617F
Initial	**F**	68	Mild anemia Thrimbocytosis	Without other disease	46,XX,dup(1)(q21q32)[15]/46,XX[15]	Didn´t reveal the presence of another chromosome	-
Revaluation		73	Mild Anemia		46,XX,dup(1)(q21q32)[30])		Not present

* The revaluation was done 59 moths after the initial diagnosis

Results

- Cytogenetics analyses for patient at initial diagnosis revealed the presence of two cell lines: 46,XX,dup(1)(q21q32)[15]/46,XX[15]. And at revaluation it was observed only the abnormal cell line (46,XX,dup(1)(q21q32)[30]) (Table 1 and Figure 1). This result was confirmed by microarray analyses.
- FISH analyses confirmed that in the chromosome 1 abnormal only exist materials of this chromosome (Table 1 and Figure 2).
- Molecular analyses of the mutation V617F in gene JAK2 revealed the absence of mutation (Table 1 and Figure 3).

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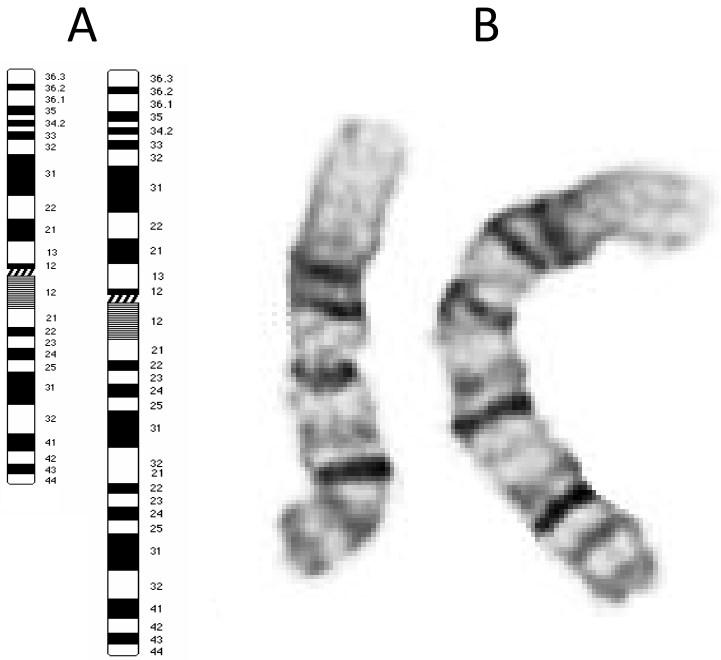

Figure 1: Chromosome 1 ideogram (**A**) and chromosomes 1, of the patient (**B**) observed in cytogenetics with G-banding staining (the ideogram/ chromosome with duplication of the region (q21q32) is on the right of each pair).

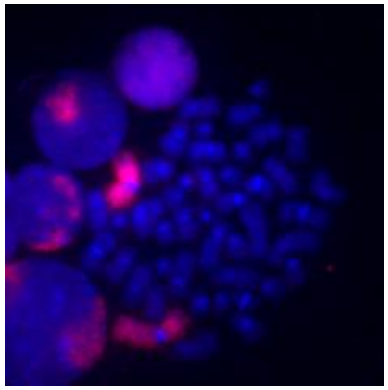

Figure 2: Partial metaphase after FISH analyses with library probe for chromosome 1 (wcp1). Both chromosomes paint integrally with probe wcp1 (red).

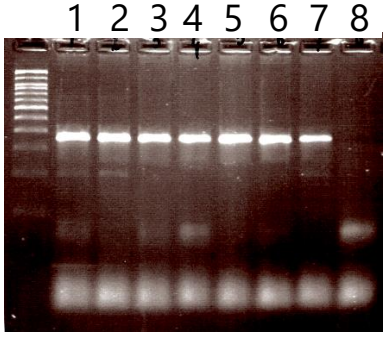

Figure 3: Results of the Multiple-PCR for the screening of the *JAK2* V617F mutation in the studied patient (lines 3 and 4). Line 7 is a control positive for the referred mutation and line 8 a control negative.

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Conclusion/Discussion

- The duplication of the region dup(1)(q21q32) associated to MN, was reported in several pathologies of this group of neoplasms[3,4,6,7]. In MPN this anomaly is associated to AML evolution.
- The presence of this duplication in different groups of MN, suggest that the duplication can occur in a precursor cell of the myeloid lineage. The region (1)(q21q32) is a rich gene region, were we can identified genes involved in the control of normal myeloid cell cycle kinetics (ex: *MNDA*) and other genes involved in the transcription (ex: *ATF6* between others). The copy number and the transcriptional activity of these amplified genes may alter the normal balance between proliferation and programmed cell death and induce the cell proliferation[5]
- Since the patient under study didn't evolves to AML, were performed studies by FISH, and high-resolution microarray, which confirmed the observed breakpoints and did not show other changes.
- Based on the patient's clinical history and results, we suggested that the duplication (1)(q21q32) alone doesn't induce an evolution to AML and the duplication of genes correlated with this pathology (ex: ARNT, among others) is not a sufficient factor for a more aggressive progression.
- However, more studies should be carried out in order to clarify the role of this alteration in NM.

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